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RELATION OF BACTERIA TO THE FAILURE OF BLOOD-VOLUME THERAPY IN TRAUMATIC SHOCK*

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EVIDENCE is offered below that bacterial action may be responsible for the failure of blood-volume therapy in various types of traumatic shock, in which infection appears to be absent or of little consequence. For an appropriate orientation to this thesis the following statement of the terms on which it is based will be helpful.

GENERAL CONSIDERATIONS

Traumatic shock is a state of acute and persisting deficiency of flow through the peripheral circulation that, if sufficiently severe and untreated, grows progressively worse and is rapidly fatal. In virtually all cases the clinical manifestations are as follows: low blood pressure, thready, rapid pulse, oliguria or anuria, cold, pale, moist skin and pale cyanotic mucous membranes. Other signs and symptoms, such as thirst, nausea, stupor and restlessness, are not consistently present and, therefore, cannot be regarded as essential components of the syndrome. The inevitable consequences of the deficient blood supply to the tissues are reflected in the following changes in the venous blood: lowered oxygen tension, increase in the concentration of lactic, pyruvic and amino acids and a concurrent decrease in carbon dioxide combining capacity. The resulting acidosis is aggravated by the accumulation of acid radicals (for example, sulfate and phosphate), derived from tissue breakdown, which cannot be eliminated because renal excretory function is impaired. Because of stagnation in the peripheral circulation there is a reduced rate of return flow from the veins to the heart, a consequent decrease in cardiac output per minute and a fall in oxygen consumption and in the basal metabolic rate.

The commonest cause of the disorder is a critical loss of blood volume (35 per cent or more), whether from hemorrhage, tissue trauma, burns or other causes. Hence, replacement of blood-volume deficit is a primary requirement in most cases. If this requirement is met by the kind of volume therapy appropriate to the circumstances, without undue loss of time, a normal circulation is promptly restored, and the chemical distortions disappear along with the clinical signs of the condition. Recovery from the shock state is heralded by a restoration of normal blood pressure, a warm, dry skin, normal color of skin and mucous membranes, and resumption of adequate urine flow.

Observers of military casualties during World War II were of the opinion that the treatment of hemorrhagic shock was a solved problem, because cure was nearly always achieved by adequate transfusions of appropriately matched blood, even those given as late as fourteen hours after the injury. This, however, is not always in accord with clinical or experimental experience.

Experimental hemorrhagic shock usually responds to blood transfusion if only hemorrhage has been employed to produce shock, if the shock period is not unduly prolonged, and if the animal is in good condition before the experiment begins and is not anesthetized or severely traumatized. But many investigators have repeatedly noted that if the animal, usually the dog, is undernourished, has fever, is sick for other reasons or is given a barbiturate or some other anesthetic, it will frequently not respond to adequate blood-volume therapy after having been in shock for some hours.

The same general considerations apply to hemorrhagic shock in man. Cases of apparently simple hemorrhagic shock fail to respond to blood transfusion. Thus, although most patients with massive bleeding from a peptic ulcer are cured by transfusion, some are not — especially if they are in the fifth or later decades of life, have been depleted by previous

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episodes of bleeding or go in and out of shock over a period of several days. The rarity of death from hemorrhagic shock among military casualties during World War II may be related to the fact that these were young, vigorous men, who responded as one expects the victim of a first massive hemorrhage from peptic ulcer to respond, provided he is of comparable age and vigor. Thus, it is necessary to take account of the general state of the victim before the hemorrhage and the duration of as well as other developments during the state of shock, to account for the occasional failure to cure hemorrhagic shock by blood transfusion.

Classifications of Shock

Many investigators believe that there are fundamental differences among the variously classified types of traumatic shock, such as "burn shock," "septic shock" and "wound shock." The clinical manifestations vary widely, but such variations are the specific effects of the particular type of trauma, and have not been shown to have any specific relation to the shock process per se. Since the hemodynamic disturbance in the peripheral circulation, as described above, appears to be much the same in all varieties of traumatic shock, a more valid basis for assuming that the process varies according to the type of trauma responsible is the differing response to blood-volume therapy. Fluid-volume therapy applied promptly is usually successful in shock due to hemorrhage or to dehydration, presumably because the primary injury producing shock is the fluid-volume deficit and nothing else. In burn shock prompt correction of the fluid-volume deficit may or may not be followed by a good response because in burns there is extensive tissue injury in addition to fluid loss. The same reservation is true of wound shock if the wounds are large, and especially when they involve the buttocks, abdomen or lower extremities. Septic shock often occurs even when there has been no significant fluid loss. Hence it should not be surprising that fluid-volume therapy usually fails in this type of shock. In short, typical traumatic shock is usually fully responsive to fluid-volume therapy when caused by hemorrhage and fully resistant when caused by sepsis, but in burn or wound shock the response may or may not be satisfactory. In hemorrhagic shock irreversibility to fluid-volume therapy develops with time, whereas in sepsis it is present to begin with. If fluid-volume deficiency were the only critical factor in hemorrhagic shock, one might expect even prolonged shock to continue to be responsive to such therapy. What other factor enters as a function of time or, in some cases, independently of the time factor to account for irreversibility, in spite of adequate replacement of the blood loss? Is the irreversibility fundamentally of the same nature in hemorrhagic shock as in septic shock and in burn shock and wound shock?

Experimental Observations

There are serious limitations to an effort to explore this problem by experimentation on the critically ill patient. Hence, the attempt has been made largely on the laboratory animal. Hemorrhagic shock, which is reversible in its early stages and may later become irreversible, is a convenient form to study experimentally. It has been utilized in an attempt to analyze the phenomenon of irreversibility; it seemed best to produce the condition with a minimum number of complicating factors. To use anesthetics on animals that are in any way depleted, or to ignore the demonstrably deleterious effects of high environmental temperature, is to introduce aggravating factors that have no direct bearing on the condition and therefore serve only to confuse the situation. Only healthy, well nourished dogs, free of fever, have been used, and the experiment has been conducted in an air-conditioned laboratory at a uniform room temperature. Even so, the need to immobilize the animal lightly and to make incisions in the groin under procaine to cannulate vessels has not been avoided. One dose of morphine is given an hour before hemorrhage is induced, since the course of events is the same as when no morphine is used; 3 to 5 cc. of heparin is given before bleeding is started.

In the standard experiment blood is allowed to run from a femoral artery into a reservoir containing a minimal quantity of heparin necessary to avoid clotting. This reservoir is a Lamson bottle elevated above the level of the heart so that bleeding stops when the systolic pressure reaches 30. The bleeding time varies from some fifteen to ninety minutes. During and after the bleeding period the dog lies quietly and exhibits the classic features of shock described above. Eventually, the blood level in the reservoir, having remained virtually stable, begins to fall (Fig. 1). The dog is taking back the shed blood because compensatory vasoconstriction is failing, and peripheral vas-

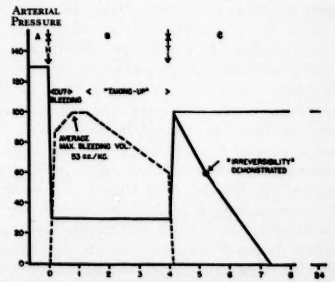

Figure 1. *Standard Experiment to Analyze the Phenomenon of Irreversible Shock (Reproduced from Fine et al.,[1] with the Permission of the Publishers).*

The solid line represents the arterial pressure, and the broken line the bleeding volume (percentage of maximum).

cular collapse is beginning. This self-transfusion tends to restore compensation, but if the systolic blood pressure cannot thereby return to and remain at 30 without the return of more blood, the self-transfusion continues. If all the blood left in the reservoir is rapidly reinfused before about 40 per cent of the total volume bled has returned spontaneously to the circulation, a permanently sustained pressor response usually occurs, and the dog recovers. The shock is reversible, and nothing more is necessary. But if 40 per cent or more of the shed blood has been taken back, the rapid return of the remainder does not cure the shock. There is a pressor response, to be sure, but, after a variable interval, pressure declines, and when it has again fallen to 60, death soon follows. This decline is a demonstration that the dog is in a state of irreversibility to transfusion. Restoration of normal blood volume is no longer sufficient. Something has happened to produce irreversibility.

The maximum amount of blood that enters the reservoir during the bleeding period averages 53 cc. per kilogram of body weight, and the average length of time elapsing between the onset of the bleeding and the spontaneous return of 40 per cent of the shed blood is about five hours.

This method for the study of hemorrhagic shock is free of the well known superimposed harmful effects of barbiturates and anesthetics on the peripheral circulation. It imposes a continuous, fixed level of severe hypotension. The load imposed is, in a real sense, a measured quantity, which is not conditioned by the action of drugs or other irrelevant factors. By the provision of a reliable means for determining the existence of a state of irreversibility to transfusion, the ability of any agent to alter that state effectively can also be determined.

More than 80 per cent of dogs subjected to hemorrhagic shock by this method die in spite of the fact that the blood volume has been returned to normal. None of the therapeutic measures that have been recommended for shock make any difference in the result, including alkali to correct acidosis, artificial dialysis to correct electrolyte imbalance, pressor drugs, including nor-epinephrine, Dibenamine to relax vasoconstrictor nerves, Coramine to increase muscle tone, thiamine to supply cocarboxylase, Cytochrome C, cortisone, DOCA and ACTH. Nor does giving more blood help in most cases.

Reasons for Failure of Transfusion Therapy

In ten years of effort to discover the reason for the failure of transfusion therapy a good deal of effort has been expended in testing existing theories. The theory that the capillaries are so damaged that much of the blood given cannot remain in the circulation was proved wrong by quantitative measurements with radioactively labeled substances.[2] The belief that disturbances in electrolyte balance were responsible was disapproved in several ways, and most effectively by the demonstration that if electrolyte imbalance is prevented or corrected, the course of events is not changed significantly.[3] Many investigators made efforts to locate the fundamental disorder in some vital organ. The central nervous system was shown to be damaged, but not critically.[4] The sympathetic nervous system was shown to remain overactive. Nor-epinephrine had some striking effects, but did not change the over-all course of events.[5] Dibenamine was of value if given well before shock was induced,[6-8] but not if given after shock had developed.[9] The somatic nerves were excluded by experiments with spinal-cord section and in other ways.[2] The heart, like the brain, stumbles a little. Its stroke output is diminished, not because the myocardium is greatly weakened, but because venous return is greatly reduced. The kidney produces little or no urine, but even total renal failure takes days to cause death, whereas shock is fatal within a few hours. The adrenal gland is excluded for the same reason, and also because adrenal hormones are quite useless. The lungs continue to function adequately right up to death. The only other vital organ that remains for consideration is the liver. In 1946 it was shown that if the liver of a dog in shock is supplied with a large flow of arterial blood by cross-circulation with a donor animal, the recipient dog does not develop irreversibility, and will respond to a transfusion after a degree and duration of shock that a control dog cannot tolerate.[10] This suggested that the liver played a key role in the phenomenon of irreversibility.

Shorr et al.[11,12] isolated a vasodepressor substance from the liver, which they considered the cause of the collapse of the circulation. They identified this substance as ferritin, a natural iron-containing protein present in many tissues, which the hypoxic liver is said to change from an oxidized to a reduced state, and which in this reduced state is said to be a vascular toxin. Since healthy dogs can excrete this substance and the healthy liver can restore it to the oxidized form, Frank and his associates[13] removed the liver and the kidneys from normal dogs, and then gave them reduced ferritin in amounts up to a thousand times the dose considered lethal, without producing any vascular depression.

It was their opinion that the liver was nevertheless at fault in some important way. Many abnormalities from impairment of the liver are present. In particular they were able to demonstrate that in shock the liver cannot synthesize proteins, such as fibrinogen and prothrombin.[14,15] This could mean loss of the ability to synthesize proteins required to detoxify poisons that might be elaborated, or drugs, like barbiturates and anesthetics, to which the organism in shock is excessively vulnerable.

On review of the evidence for endogenous and exogenous toxins, the possibility that bacterial toxins might be affecting the course of hemorrhagic shock adversely appeared to deserve further investigation.

Aub and his associates[16,17] had demonstrated that clostridial toxins, isolated from tourniqueted dog muscle, could produce hemolysis and vascular collapse. None of the experiments on hemorrhagic shock by me and my co-workers or by anyone else, to my knowledge, had been done with strict sterile precautions. This was not surprising because even if bacteria were present, it seemed unlikely that they could develop a lethal dose of toxin in such a short time. Nevertheless, the experiments were repeated with all the precautions taken in a modern operating suite, and no change whatever in the course of events was found, indicating that bacteria were not being introduced. But what of the bacteria normally found in the dog's tissues? The presence of clostridia in the liver of every normal healthy dog is a well known fact. The possibility that these organisms were elaborating a vascular toxin was tested by the administration of penicillin during shock. The result (40 per cent recovery) was a distinct, but not sufficiently striking, improvement in survival rate to be decisive. The same change in survival rate was achieved with chlortetracycline given intravenously during shock.

During these investigations the authors were occupied with other problems dealing with conditions that can excite the invasion of intestinal bacteria. Many investigators[18-20] had observed invasion by intestinal bacteria as a result of irritation of intestinal mucosa by acid or of other types of injury to the gut. Schweinburg et al.[21] had shown that *Escherichia coli* can migrate from the gut to the peritoneum and produce peritonitis when the peritoneum in uremic animals is irrigated with a modified Ringer solution. Since invasion from the gut exposed to the hypoxia of shock for several hours was also conceivable, the effect of chlortetracycline given orally to forestall such an invasion, if it was occurring during shock, was tested. This was done by the administration of 5 gm. of chlortetracycline glycinate daily for six days in advance of the experiment. An additional 5 gm. (priming dose) was given in solution by gavage on the day of the experiment, several hours before the induction of shock, to assure a substantial inhibition of intraintestinal bacteria during the shock period. The same method was employed with neomycin, oxytetracycline and other chemotherapeutic drugs, in what are regarded as therapeutically equivalent doses. For every experiment in which a group of dogs received an antibiotic, at least 1 untreated dog was run simultaneously as a control.

In the first series of 25 dogs treated with chlortetracycline by mouth as described a clearly beneficial effect was obtained—that is, a survival rate of over 80 per cent as compared with one of 20 per cent in 25 untreated dogs run concurrently.[22] This experiment was repeated with neomycin and oxytetracycline, with nearly the same results. Penicillin given via a duodenal catheter was also effective, though less satisfactory than the other antibiotics.

Since chlortetracycline, oxytetracycline, neomycin* and penicillin are absorbable drugs, one cannot attribute their action exclusively to an effect on intraintestinal bacteria. In a further effort to assess the role of the intestinal flora three virtually non-absorbable antibacterial drugs, polymyxin, bacitracin and sulfathalidine, were tested. Although results were poor, these agents were not wholly without effect.[23]

The effect of these antibiotics given via the systemic veins were then studied. Since the liver is more heavily contaminated than any other tissue, these drugs were also administered through the portal vein. The infusion, started three hours before shock and completed within an hour, was more effective than that started shortly before the hemorrhage and continued during shock. The best results by either the portal or the systemic route were nearly as good as those achieved by the oral route.[23]† Therefore, the effect of the antibiotics appears to be achieved, not by the suppression of intraintestinal bacteria, but by the suppression of toxin production by bacteria in the tissues.

No explanation can be offered for the lack of correlation between effectiveness in shock and the known antibacterial range of the various antibiotics tested. It is significant, however, that antibiotics with the broadest range are required for maximum protection. But the protection is not maximal unless it is provided before the shock state is induced. If the antibiotic is not administered until irreversibility has set in, there is no protection. Since the presence in the tissues of an effective concentration of antibiotic is required at the time shock is induced, the relative ineffectiveness of such therapy during shock may be because, first, access of the drug to the tissues is hindered by poor flow through the peripheral vascular bed, secondly, a lethal dose of bacterial toxin is produced early in shock or, thirdly, a small fraction of an ordinarily lethal dose, produced before the antibiotic is given, is sufficient to kill because of a greatly increased susceptibility to bacterial toxin.

Thus far the evidence that bacterial action may complicate hemorrhagic shock and be responsible for the development of irreversibility to transfusion is inferential, — that is, one assumes that if antibiotics protect the subject, they do so by virtue of their antibacterial properties. Available, but as yet unpublished data,[24,25] which I will not present here, demonstrate that the effective antibiotics do indeed act as antibacterial agents, and not because of some other protective pharmacologic property. More direct evidence that irreversibility to transfusion is due to bacterial action[26] is as follows:

> One hundred and fifty cubic centimeters of a thick saline suspension of liver, made from a mash of 200 gm. of normal liver, was injected intraperi-

*Three per cent of this highly potent drug is absorbed. This may be sufficient against sensitive bacteria.

†Antibiotics that failed by the oral route were no better when given through the portal vein.

toneally into normal dogs, with a resulting recovery rate of 70 per cent. The animals that died did not show gross peritonitis, but a little bloody fluid containing clostridia, present in the mash, and *Esch. coli*, not present in the mash, was found. The same results were obtained with "shocked" liver, — that is, liver obtained from dogs dying of irreversible hemorrhagic shock. These experiments were repeated in dogs in hemorrhagic shock for two hours, after which they were transfused. Ordinarily, the recovery rate for two-hour shock is virtually 100 per cent. Ninety per cent of dogs in two-hour shock that had received the "normal" liver mash recovered; the response to transfusion was the usual satisfactory one, and the dogs remained well. All the dogs subjected to two-hour shock that received the "shocked" liver mash also responded satisfactorily to transfusion, but they were all dead in about eighteen hours, and showed the intraperitoneal findings described above. The "shocked" liver mash, therefore, contained a factor that was not lethal for normal dogs but was lethal for dogs in shock, from which they otherwise would have recovered. This lethal factor was shown to be of bacterial origin by the observation that 70 per cent of the recipient dogs recovered from two-hour shock when they were treated with penicillin.

These observations demonstrate that the bacteria in the liver of a dog in shock increase in virulence as a consequence of a state of shock that is allowed to persist long enough. Since the toxin production resulting from this increase in virulence, although relatively harmless to a healthy dog, is lethal for a dog exposed to a relatively brief period of shock, it follows that the donor of the "shocked" liver, subjected to the same increase in virulence, also fails to recover after transfusion and dies because of bacterial activity. Since this donor is exposed to the bacterial activity in its entire liver,* it is not surprising that it dies sooner (six hours more or less) than a dog in shock that is still reversible and exposed to only 200 gm. of liver (eighteen hours more or less). No other factor than bacterial toxin is needed to explain the donor dog's irreversibility, in view of the fact that irreversibility can be prevented by appropriate antibiotic therapy.

The species of bacteria responsible for the bacterial toxins that produce irreversibility to transfusion have not been identified. During life cultures of blood from the shocked dog are sterile, whereas those from the tissues yield clostridia. But immediately after death about 25 per cent of the cultures from blood and tissues show gram-negative and gram-positive bacteria, all of which are intestinal flora. The clostridia alone cannot be incriminated because polyvalent gas-bacillus antitoxin or immunization with polyvalent clostridial toxoid do not offer protection, whereas neomycin, which does not affect the clostridia, does protect the animal. However, identification of the particular species of bacteria involved is not so important as the fact that bacterial action accounts for irreversibility in hemorrhagic shock in dogs.

Why do the bacteria in the tissues trouble the shocked dog but not the healthy dog? The following experiments show that this is because *the dog in shock has lost its antibacterial defense mechanisms.*[25]

A twenty-four-hour growth of *Esch. coli* or a hemolytic coagulase-positive staphylococcus (5,000,000,000 to 50,000,000,000) was injected intravenously into healthy dogs. The blood was cleared exponentially, so that within six hours not over 10 bacteria per cubic centimeter of circulating blood remained. After twenty-four hours the blood was sterile, and all the dogs recovered. Cultures of the tissues of these dogs, killed after another day or two, were free of the injected bacteria. *Clostridium welchii* was also tested. This organism was disposed of a little less well, but the findings were substantially the same, except that the tissues showed *Cl. welchii*, as in the normal dog.

These experiments were then performed in dogs subjected to severe and prolonged hemorrhagic shock — that is, shock that was allowed to become irreversible to transfusion. The blood was cleared in many such animals as well as in normal ones, but in about 40 per cent the clearance was only partial or failed altogether, so that by the sixth hour bacterial multiplication in the blood was proceeding.

The same experiment was then performed in dogs subjected to two-hour shock. In these dogs the course of events was dramatically different. The immediate reaction to the transfusion was the customary one. A good pressor response occurred, shock disappeared, and for the ensuing twelve hours or so the animals seemed well. Moreover, the blood clearance curve was substantially, if not quite, as good as that in normal dogs. On the following day, however, they were obviously ill, and the blood cultures were uniformly positive for the injected bacteria. Cultures continued to be positive thereafter, and all but 1 of the entire series died within twenty-four to ninety-six hours. Cultures of the blood, liver and spleen at death were positive for the injected bacteria.

From these data it is evident that the scavenger action of the blood during the first six hours after injection of the bacteria is not seriously interfered with, but the antibacterial mechanisms are severely damaged.

How long does this gross damage persist? To answer this question 5 different series of dogs were subjected to two-hour shock, and the bacteria injected immediately after transfusion or twelve, twenty-four, thirty-six or forty-eight hours after the transfusion. All those injected at twelve hours died. Those in the twenty-four-hour series were very sick or dying

*Since many tissues in the dog normally harbor bacteria the liver is not the sole or even the major source of bacterial toxin in hemorrhagic shock. One may expect the hypoxia of hemorrhagic shock to be capable of exciting bacterial activity in muscle, just as it does in liver. That this is so was shown by injection of muscle mash intraperitoneally. "Normal" muscle mash produced a 20 per cent mortality in dogs subjected to 2-hour shock, but "shocked" muscle mash was uniformly fatal in others, in which the intraperitoneal findings at autopsy were the same as those produced by "shocked" liver mash.

at the time they were killed. The cultural data were the same as those for dogs injected after an hour in shock. Whereas most of the thirty-six-hour dogs survived, the cultural data showed that the antibacterial function had not yet fully recovered. All the forty-eight-hour dogs survived, but with partial impairment of this function still in evidence.

Discussion

Since *Esch. coli*, which in the healthy dog is relatively nonvirulent, possesses lethal power in a dog subjected to hemorrhagic shock of only two hours' duration, the antibacterial defense must be considered to be virtually abolished. Relapse into shock, which sometimes follows a good initial response to blood-volume therapy, may be due to continuing loss of blood volume. When it cannot be so accounted for, one should consider the evidence given that in the recovery phase the organism continues to be more vulnerable than usual to bacterial activity because of the slow return of the normal antibacterial potential.

A possible explanation for the collapse of this vital function is the failure of protein synthesis in shock. Thus, when the circulation of the healthy dog is depleted of fibrinogen or prothrombin, the normal titer is restored in about sixty hours. After hemorrhagic shock lasting only an hour, this interval is prolonged to one hundred and eighty to two hundred and forty hours. If the continuous production of certain proteins (for example, enzymes in the reticuloendothelial system, and immune globulins) necessary for effective antibacterial defense is similarly interfered with, one can expect a poor to absent defense against bacteria not only during the shock state but also for some days afterward.

Since the dog is a species that normally harbors bacteria in its tissues, what relevance do these observations have for species whose tissues are normally sterile? In oligemic shock associated with open wounds or burns, where bacterial contamination can be taken for granted, these observations are relevant. Even in the absence of such obvious portals of entry, a sterile species can be subject to the effects of bacterial action during oligemic shock.[26] Thus, the normal tissues of the white rat are sterile. The muscles of the tourniqueted extremities of the rat are also sterile as long as the tourniquet remains applied, even up to twenty-four hours. But within two or three hours of removal of the tourniquet clostridia begin to appear in these muscles. Twenty-four to forty-eight hours later cultures of the injured muscles are uniformly positive for clostridia, whereas the tissues proximal to the site of application of the tourniquets remain sterile.

These observations demonstrate that clostridia normally invade from the intestine even in a sterile species, but that they do not survive in healthy tissues because of a naturally effective bactericidal defense, which is lost only in the injured tissues.* Since the rat in hemorrhagic shock, produced by the same technic as for the dog, is also protected by antibiotics,[26] it appears that irreversibility to transfusion in the rat may also be due to bacteria. Bacteria have not been demonstrated in the tissues of shocked rats immediately after death from ineffective transfusion, but some hours after death 25 per cent of the cultures of the back muscles are positive for clostridia. The barriers to invasion are presumably far from solid in both rat and dog. Hence, these species differ not so much in the firmness of these barriers as in their ability to destroy bacteria after invasion. If this faculty is lost in the rat, as it is in the dog, as a result of hemorrhagic shock, such bacteria may acquire sufficient virulence to be lethal.

If these considerations of the development of irreversibility to transfusion in hemorrhagic shock are valid, they are even more so when fluid-volume therapy fails in shock associated with open wounds, burns or other types of massive tissue injury in which bacterial contamination may be taken for granted. For such a failure may signify that the refractory state is due to a bacterial factor that has become operative in the meantime.

It is said that refractoriness to fluid-volume therapy is frequently present in the absence of any evidence of bacterial activity. But conclusive evidence required to exclude a bacterial factor is far more than has been adduced. The exclusion of bacterial action cannot be affirmed by the absence of the usual local or constitutional responses to infection, since these require the mobilization of defense mechanisms that are demonstrably weakened in shock.[26-29] If a wound is present much more testing than is commonly done would be required to exclude the action of pathogenic bacteria as a cause for a refractory response to adequate fluid-volume therapy. Even when fully exploited, ordinary clinical technics for assessing the presence of pathogenic bacteria and their toxicity may not suffice, for the experimental data demonstrate that vascular collapse may be the only evidence of the toxic action of bacteria.

It is necessary to consider not only obvious bacterial contamination of wounds, but also the possibility of invasion across presumably intact barriers, such as the respiratory and gastrointestinal tracts. Invasion of the body by bacteria even in the healthy state is probably going on continuously.[30-32] Otherwise, it would be difficult to explain the constant presence of intestinal bacteria in the tissues of the dog and other species or, in man, the deposition of bacteria (usually intestinal flora) at sites of obstruction to the continuous flow of fluids, as in ureteral stricture or choledocholithiasis.

This does not imply that peripheral vascular collapse, which persists after replacement of a fluid-vol-

*It has been also observed that a strain of *Streptococcus viridans*, given to a rat orally or intravenously, can be recovered from the tourniqueted muscles, but from no other tissues, even if the shock that normally follows is prevented by prompt and adequate fluid therapy.[26]

ume deficit or which occurs in the absence of such a deficit, is always due to a bacterial toxin. Presumably many toxins are capable of causing shock that will not yield to fluid-volume therapy. But if prolonged hemorrhagic shock, by virtue of the loss of antibacterial defense mechanisms, can invite the added burden of shock due to bacterial action, the same thing may happen in severe and prolonged shock produced by any agent. Therefore, in the treatment of traumatic shock, however induced, that persists in spite of a restored fluid balance, one should consider the possibility that a superimposed bacterial activity is operating, however remote its likelihood from the evidence that existing methods of detection provide.

Conclusion

From the experimental data presented the benefit to be expected from antibiotic therapy in shock will depend, as in any infection, not only on the susceptibility of the offending bacteria to the antibiotic employed but also on the amount of toxin that has been released before the delivery of an adequate concentration of the appropriate antibiotic to the sites of bacterial action and finally on the extent to which the normal antibacterial defenses have been impaired.

References

1. Fine, J., Frank, H., Schweinburg, F., Jacob, S., and Gordon, T. Bacterial factor in traumatic shock. *Ann. New York Acad. Sc.* **55**: 429-445, 1952.
2. Fine, J., and Seligman, A. M. Traumatic shock. VII. Study of problem of "lost plasma" in hemorrhagic, tourniquet, and burn shock by use of radioactive iodo-plasma protein. *J. Clin. Investigation* **23**:720-730, 1944.
3. Frank, H. A., et al. Traumatic shock. XX. Course of hemorrhagic shock in dogs treated by peritoneal irrigation or by artificial kidney. *Am. J. Physiol.* **168**:140-149, 1952.
4. Phemister, D. B. Role of nervous system in shock. *Ann. Surg.* **118**: 256-267, 1943.
5. Frank, E. D., et al. Unpublished data.
6. Wiggers, H. C., Ingraham, R. C., Roemhild, F., and Goldberg, H. Vasoconstriction and development of irreversible hemorrhagic shock. *Am. J. Physiol.* **153**:511-520, 1948.
7. Remington, J. W., Wheeler, N. C., Boyd, G. H., Jr., and Caddell, H. M. Protective action of dibenamine after hemorrhage and after muscle trauma. *Proc. Soc. Exper. Biol. & Med.* **69**:150, 1948.
8. Remington, J. W. Nervous system in shock. In *First Conference on Shock and Circulatory Homeostasis, October 22-23, 1951, New York, New York.* 245 pp. Edited by H. D. Green. New York: Josiah Macy, Jr., Foundation, 1952. Pp. 73-114.
9. Friedman, E. W., et al. Unpublished data.
10. Frank, H. A., Seligman, A. M., and Fine, J. Traumatic shock. XIII. Prevention of irreversibility in hemorrhagic shock by viviperfusion of liver. *J. Clin. Investigation* **25**:22-29,1946.
11. Shorr, E., Zweifach, B. W., Furchgott, R. F., and Baez, S. Hepatorenal factors in circulatory homeostasis: tissue origins of vasotropic principles, VEM and VDM, which appear during evolution of hemorrhagic and tourniquet shock. *Circulation* **3**:42-79, 1951.
12. Mazur, A., Litt, I., and Shorr, E. Relation of sulfhydryl groups in ferritin to its vasodepressor activity. *J. Biol. Chem.* **187**:485-495, 1950.
13. Frank, H. A., et al. Traumatic shock. XXII. Irreversibility of hemorrhagic shock and VDM hypothesis: failure of ferritin to affect arterial pressure and survival period of hepatectomized-nephrectomized dogs. *Am. J. Physiol.* **168**:150-155, 1952.
14. Frank, E. D., Frank, H. A., and Fine, J. Traumatic shock: plasma prothrombin activity in hemorrhagic shock in dog. *Am. J. Physiol.* **167**:499-507, 1951.
15. *Idem.* Traumatic shock: plasma fibrinogen in hemorrhagic shock in dog. *Am. J. Physiol.* **162**:619-631, 1950.
16. Aub, J. C. Toxic factor in experimental traumatic shock. *New Eng. J. Med.* **231**:71-75, 1944.
17. Nathanson, I. T., et al. Toxic factor in experimental traumatic shock: physiologic effects of muscle ligation in dog. *J. Clin. Investigation* **24**:829-834, 1945.
18. Arnold, L. Passage of living bacteria through wall of intestine and influence of diet and climate upon intestinal auto-infection. *Am. J. Hyg.* **8**:604-632, 1928.
19. Cirrincione, F. A., and Francona, A. Influence of vascular impairment on absorption of bacteria into blood from upper intestinal tract. *Proc. Soc. Exper. Biol. & Med.* **29**:400, 1932.
20. Rabinovici, N., and Fine, J. Effect of aureomycin on intestine subjected to vascular injury. *Ann. Surg.* **135**:344-366, 1952.
21. Schweinburg, F. B., Seligman, A. M., and Fine, J. Transmural migration of intestinal bacteria: study based on use of radioactive *Escherichia coli*. *New Eng. J. Med.* **242**:747-751, 1950.
22. Frank, H. A., Jacob, S. W., Schweinburg, F. B., Goddard, J., and Fine, J. Traumatic shock. XXI. Effectiveness of antibiotic in experimental hemorrhagic shock. *Am. J. Physiol.* **168**:430-436, 1952.
23. Jacob, S., et al. Unpublished data.
24. Fine, J. *The Bacterial Factor in Traumatic Shock.* 78 pp. and index. Springfield, Illinois: Thomas, 1954.
25. Schweinburg, F. S., Friedman, E. W., and Fine, J. Unpublished data.
26. Schweinburg, F. B., Frank, H. A., and Fine, J. Unpublished data.
27. Friedman, E. W., Schweinburg, F. B., Yashar, J., and Fine, J. Unpublished data.
28. Miles, A. A., and Niven, J. S. F. Enhancement of infection during shock produced by bacterial toxins and other agents. *Brit. J. Exper. Path.* **31**:73-95, 1950.
29. Mahoney, E. B., Howland, J. W., and Yackel, K. Role of infection in shock produced by muscle injury. *Surgery* **17**:805-815, 1945.
30. Murray, M., and Moosnick, F. Incidence of bacteremia in patients with dental disease. *J. Lab. & Clin. Med.* **26**:801, 1941.
31. Okell, C. C., and Elliott, S. D. Bacteremia and oral sepsis, with special reference to aetiology of subacute endocarditis. *Lancet* **2**: 869-872, 1935.
32. Kotin, P. Technics and interpretation of routine blood cultures: observations in five thousand consecutive patients. *J.A.M.A.* **149**: 1273-1276, 1952.

APPENDICITIS IN CHILDREN

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BOSTON

REVIEW was made of all children under thirteen years of age subjected to appendectomy at the Boston City Hospital from January 1, 1950, to January 1, 1953. Included in this series, which totaled 405 cases, were 43 in which elective "interval appendectomy" was performed. The findings in this subgroup, including the rate of diagnostic error, were taken into account in all calculations. Objection may be made to the inclusion of "interval appendectomy" in this series on the ground that this procedure does not represent surgery for appendicitis. We believe that this point is technically correct but unrealistic. From a practical standpoint, in our opinion, "interval appendectomy" does represent a definite, if small, part of the problem of appendicitis: the surgeon operates to remove an appendage that is troublesome, if not inflamed, hoping by this means to alleviate symptoms or reduce the mortality and morbidity of appendicitis.

All patients were examined by at least one member of the visiting staff before operation. The vast majority of operations were performed by members of the house staff. The pathologist's gross and microscopi-

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cal diagnoses were regarded as final on all specimens submitted. In this entire series there was but 1 fatal case, the death on the operating table of a seven-year-old child with a ruptured appendix who was given a spinal anesthetic. Forty-five minutes after administration of the anesthesia cardiac arrest occurred that did not respond to the usual methods of resuscitation, including cardiac massage. The overall mortality rate was thus 0.24 per cent.

Some form of appendiceal disease was found in 74.07 per cent of the children in this series. Thus, there was a diagnostic error of 25.9 per cent, which is designated the rate of "negative" diagnostic error, since the operative findings in this 25.9 per cent were negative for appendicitis. The final diagnoses of all cases are listed in Table 1. Of the group with a finding of appendiceal disease at operation 2 out of 3 had acute appendicitis only, 1 in 5 showed perforation without abscess, and 1 in 13 had frank abscess formation. Among the 105 patients without appendiceal disease approximately 1 in 3 had no demonstrable abnormality at operation, whereas 4 in 7 were concluded to have mesenteric adenitis — a diagnosis admittedly open to some question. Three children with tubal disease had symptoms and signs easily confused with appendicitis, each having a present illness of less than twenty-four hours. Likewise, the patients with ruptured ovarian cyst, Meckel's diverticulum with volvulus, abscess of the ileal mesentery and primary peritonitis presented clinical and laboratory findings similar to those observed in appendicitis.

TABLE 1. *Final Diagnoses in 405 Children Subjected to Appendectomy.*

DIAGNOSIS	NO. OF CASES	
Acute appendicitis	205	(50.63%)
Perforated appendix	60	(14.82%)
Mesenteric adenitis	60	(14.82%)
No finding	30	(7.40%)
Appendiceal abscess	23	(5.66%)
Oxyuris infestation	8	(1.98%)
Dysmenorrhea	3	
Salpingitis	3	
Adhesions of appendix	3	
Ruptured ovarian cyst	2	
Meckel's diverticulum, with volvulus	1	
Abscess of ileal mesentery	1	
Trigonitis	1	
Primary peritonitis	1	
Gastroenteritis	1	
Full bladder	1	
Chronic appendicitis	1	
Pyelonephritis	1	
Total	405	

On the other hand 3 patients with dysmenorrhea were subjected to appendectomy during the second day of their menses. Operation might have been avoided in 4 patients with trigonitis, gastroenteritis, pyelonephritis and overdistended bladder if they had been more carefully evaluated. This group of 7 cases we consider to represent "obviously avoidable" diagnostic error. The rate of obviously avoidable, negative diagnostic error for this series was thus 1.7 per cent.

AGE DISTRIBUTION

The case distribution according to age for the various forms of appendicitis and for mesenteric adenitis is shown in Figure 1. In this series appendicitis did not occur under two years or mesenteric adenitis under three years of age. The number of cases of acute appendicitis increased almost steadily for each year of life after two years. Mesenteric adenitis, on the other hand, was relatively infrequent until the sixth year, when its incidence began to rise sharply, reaching a maximum in the eighth year of life; thereafter it remained at a relatively constant level. Appendiceal abscess appeared to be most frequent in the fourth year of life in this series.

SEX DISTRIBUTION

In acute appendicitis and appendiceal abscess, males outnumbered females in a ratio of 2:1. This ratio was reversed in the cases in which no disease was found and was equal for both sexes in mesenteric adenitis and perforated appendix.

DURATION OF SYMPTOMS

The duration of the present illness before admission in the various forms of appendiceal disease and in so-called mesenteric adenitis is compared in Table 2.

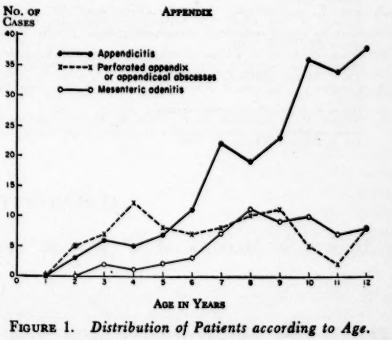

FIGURE 1. *Distribution of Patients according to Age.*

Only 13.8 per cent of patients with acute appendicitis had a present illness extending beyond forty-eight hours as compared to 31.6 per cent of those with perforated appendix and 54.6 per cent of those with appendiceal abscess.

SYMPTOMS AND SIGNS

The frequency of major symptoms and signs and the laboratory findings among all patients with appendicitis in some form or with mesenteric adenitis are presented in Table 3.

Abdominal pain was frequently difficult or impossible to localize in the younger age groups; nevertheless, in all but 6 patients, or 97.7 per cent, with some form of appendiceal disease a history or suggestion of abdominal pain could be elicited. Pain was localized in the right lower quadrant in 70.7 per cent of the patients with acute appendicitis, 50 per cent with mesenteric adenitis and only 26.7 per cent with perforated appendix. The classic shift of pain from periumbilical region to right lower quadrant occurred in 39 per cent of the patients with acute appendicitis, 11.6 per cent with mesenteric adenitis and only 1.7 per cent with perforated appendix, and was not found in any with appendiceal abscess; one wonders if this low incidence in the cases of perforated appendix and appendiceal abscess is not an outstanding reason for the delay in hospitalization of these patients.

TABLE 2. *Duration of Illness.*

DIAGNOSIS MADE AT OPERATION	NO. OF CASES	DURATION UP TO 24 HR.	DURATION OF 24 TO 48 HR.	DURATION OF 48 TO 72 HR.	DURATION OVER 72 HR.
		%	%	%	%
Acute appendicitis	205	66.2	20.0	8.7	5.1
Mesenteric adenitis	60	52.7	12.0	12.0	23.3
Ruptured appendix	60	31.7	36.7	25.0	6.6
Appendiceal abscess	23	9.0	36.4	18.2	36.4

A history of nausea was difficult to evaluate in this series. Vomiting occurred in 93.3 per cent of the patients with perforated appendix, 75.1 per cent with acute appendicitis, 65.2 per cent with appendiceal abscess and 53.3 per cent with mesenteric adenitis. A history of constipation was significantly more frequent in those showing appendiceal disease at operation. A history of diarrhea was most commonly elicited in patients with perforated appendix or appendiceal abscess.

No remarkable variation in the incidence of respiratory infection was noted between the patients with various forms of appendicitis and those with mesenteric adenitis.

Abdominal tenderness was extremely common in all groups in this series. However, spasm of the abdominal musculature was recorded in 73.4 per cent of the patients with acute appendicitis, 93.3 per cent with perforated appendix, 56.5 per cent with appendiceal abscess and only 11.6 per cent with mesenteric adenitis.

Peristalsis, on auscultation of the abdomen, was frequently diminished in patients with appendiceal abscess, and almost invariably diminished in those with perforated appendix. In no patient with perforated appendix was there increased peristalsis; absent peristalsis was most frequent in these cases and was never found with mesenteric adenitis.

The clinical temperature was found to be elevated in 83.3 per cent of patients with perforated appendix and 91.3 per cent with appendiceal abscess, but was of no value in differentiating acute appendicitis from mesenteric adenitis, since elevations were equally distributed between these two groups.

The white-cell count was considered to be within normal range if it was below 12,000. By this criterion, elevated counts were seen in 92.4 per cent of patients with perforated appendix, 87 per cent with appendiceal abscess and 80.5 per cent with acute appendicitis. On the other hand, the count was elevated in only 43.5 per cent of patients with mesenteric adenitis.

Of this entire series 12 patients with appendiceal disease at operation were found to have been in the hospital for more than twelve hours before surgery. The records of all 12 were carefully reviewed, pertinent findings appearing in Table 4. In 11 an incorrect diagnosis was made on admission, and operation inadvertently deferred from fifteen hours to five days. It will be noted that in every one of the cases misdiagnosed on entry the patient complained of abdominal pain, and all but 1 had an elevation of temperature or vomiting, or both; only 1 showed no abdominal tenderness, and only 1 failed to have a leukocytosis. An incorrect diagnosis of mesenteric adenitis was made in 5 of these cases, and one of acute upper respiratory infection, gastroenteritis and pyelitis in 2 cases each.

In addition to these 11 patients with some form of appendicitis misdiagnosed at the time of admission 4 operated on electively for "interval appendectomy" were found to have acute or subacute appendicitis at the time of laparotomy. The errors of diagnosis herein represented are termed "positive," and the rate of "positive" diagnostic error for this series was thus 4 per cent.

INTERVAL APPENDECTOMY

Study of the 43 patients undergoing "interval appendectomy" included a two-year follow-up questionnaire sent to all parents. Of these patients 5 had appendicitis, which was acute in 2, subacute in 2 and chronic in 1, and in 3 oxyuris infestation was found by the pathologist. Of the remainder, 4 were reported to have bands or adhesions of the appendix, 17 mes-

enteric adenitis, and 14 no positive findings whatsoever at operation. All patients in this group gave a history of one or more episodes of acute abdominal pain before operation. Among the 31 patients showing no disease of the appendix in this group, the parents of 24 could be located; 7 could not be traced. Results of the questionnaire sent out to the parents are presented in Table 5. Twenty of the 24 children in this group were considered by their parents to be better after interval appendectomy, and only 1 was considered to have received no benefit from the operation.

TABLE 3. *Incidence of Major Clinical and Laboratory Findings.**

Final Diagnosis	Sex		Abdominal Pain			Nausea	Vomiting	Constipation	Diarrhea	Upper Respiratory Infection	Abdominal Tenderness	Spasm	Rebound Tenderness
	M	F	General Umbilical	Right Lower Quadrant	Shifting								
	%	%	%	%	%	%	%	%	%	%	%	%	%
Acute appendicitis	62.9	37.1	28.3	70.7	39.0	56.6	75.1	16.1	9.2	23.4	95.6	73.4	51.4
Mesenteric adenitis	55.0	45.0	48.3	50.0	11.6	46.6	53.3	1.6	11.6	26.6	90.0	11.6	16.7
Perforated appendix	51.7	48.3	71.7	26.7	1.7	33.3	93.3	21.7	20.0	16.7	93.3	93.3	58.7
No abdominal lesion	35.1	64.9	43.2	56.7	24.3	30.0	40.6	10.7	8.1	24.3	78.3	21.7	27.0
Appendiceal abscess	69.5	30.5	82.6	34.8	—	39.1	65.2	17.4	21.7	17.4	87.0	56.5	56.5

*Figures represent percentage of total in each diagnostic group.

Discussion

The rates of diagnostic error and of mortality were of prime interest in this survey. Diagnostic error was classified as negative when the patient was mistakenly thought to have disease and positive when unsuspected

TABLE 4. *Data on Patients with Delayed Operation.*

Case No.	Age	Sex	Diagnosis on Admission	Pathological Diagnosis	Nausea	Vomiting	Right Lower-Quadrant Pain	Periumbilical Pain	Shifting Pain	Upper Respiratory Infection
	yr.									
1*	4	F	Appendiceal abscess	Appendiceal abscess	Absent	Absent	Absent	Present	Absent	Absent
2	9	M	Pharyngitis; (?) viral disease.	Appendiceal abscess	Present	Present	Absent	Present	Absent	Present
3	12	M	Gastroenteritis	Appendiceal abscess	Absent	Present	Absent	Present	Absent	Absent
4	9	F	Mesenteric adenitis	Appendiceal abscess	Absent	Present	Absent	Present	Absent	Present
5	7	F	Pyelitis; mesenteric adenitis.	Appendiceal abscess	Absent	Present	Absent	Present	Absent	Absent
6	4	F	Upper respiratory infection; gastroenteritis.	Appendiceal abscess	Present	Present	Present	Present	Absent	Present
7	6	M	Mesenteric adenitis	Perforated appendix	Absent	Present	Absent	Present	Absent	Absent
8	12	F	Pyelonephritis	Perforated appendix	Absent	Present	Present	Present	Absent	Absent
9	7	F	Mesenteric adenitis	Perforated appendix	Absent	Present	Present	Present	Absent	Absent
10	11	M	Pharyngitis; mesenteric adenitis.	Acute appendicitis	Absent	Absent	Absent	Present	Absent	Present
11	12	F	Ruptured corpus hemorrhagicum	Acute appendicitis	Present	Absent	Present	Absent	Absent	Absent
12	9	F	—†	Early acute appendicitis	Absent	Present	Absent	Present	Absent	Absent

*Operation deferred for preparation.
†Diagnosis delayed by lack of signs.

appendicitis was found. It is our belief that, although the rate of diagnostic error must be kept as low as possible, overemphasis on a low rate of negative diagnostic error may increase the rate of positive diagnostic error, whereby the mortality rate from appendiceal disease per se will be increased. This is particularly true in children, in whom the symptoms and signs of appendicitis may be bizarre or minimal. The rate of negative diagnostic error in this series of 405 cases was 25.9 per cent, a figure almost identical with that reported by Ward-McQuaid[1] in 500 cases. An effort must be made to lower this rate. Nevertheless, we wonder if attempts to reduce it to a level of 2 per cent, as recently suggested,[2] would not increase the rate of positive error and thus the mortality rate of appendicitis. In this series the only fatal case occurred in a seven-year-old child on the operating table after administration of a spinal anesthetic. In this regard

TABLE 3 *(Concluded).*

Rectal Tenderness	Normal White-Cell Count	Elevated White-Cell Count	Absent Peristalsis	Diminished Peristalsis	Increased Peristalsis	Subnormal Temperature	Normal Temperature	Elevated Temperature
%	%	%	%	%	%	%	%	%
67.3	19.5	80.5	6.3	16.1	5.9	4.9	30.2	62.9
50.0	56.5	43.5	—	6.6	5.0	6.6	31.6	61.6
75.0	7.6	92.4	26.7	30.0	—	—	16.7	83.3
64.8	54.1	21.6	2.7	8.1	10.7	2.7	40.6	56.7
8.7	13.0	87.0	13.0	34.8	8.7	8.7	—	91.3

TABLE 4 *(Concluded).*

Temperature °F.	Pulse	Diarrhea	Constipation	Abdominal Tenderness	Spasm	Rebound Tenderness	Peristalsis	Rectal Tenderness	Duration of Symptoms *days*	Delay Before Operation *hr.*	White-Cell Count *x10²*
102.0	110	Absent	Absent	Present	Absent	Absent	Diminished	Absent	10	14	25.0
101.8	138	Absent	Absent	Present	Absent	Absent	Normal	Present	2	73	11.7
102.8	112	Present	Absent	Present	Absent	Absent	Normal	Absent	21	120	12.3
102.0	94	Absent	Absent	Absent	Absent	Absent	Normal	Absent	2	16	12.5
101.4	136	Absent	Absent	Present	Absent	Present	Diminished	Absent	2	15	20.0
104.6	80	Absent	Absent	Present	Absent	Absent	Increased	Absent	14	17	17.8
100.4	100	Absent	Absent	Present	Absent	Absent	Normal	Present	3	20	12.0
98.2	90	Absent	Present	Present	Absent	Absent	Normal	Absent	1	24	14.4
98.6	120	Absent	Present	Present	Absent	Absent	Normal	Present	2	24	16.8
98.0	—	Absent	Absent	Present	Absent	Absent	Normal	Absent	1	120	12.5
99.8	94	Absent	Absent	Present	Absent	Absent	Normal	Absent	½	36	14.1
101.0	90	Absent	Absent	Present	Present	Absent	Normal	Absent	2	24	—

we heartily agree with Gross[3] that ether anesthesia is the anesthesia of choice in children. The over-all mortality of 0.24 per cent was precisely that described by McLanahan.[4]

TABLE 5. *Results of Operation according to Questionnaires Returned for 24 Children.*

RESULT	NO. OF CASES
Child felt better after operation	20
Child felt worse after operation	0
Child felt same after operation	4
No pain since operation	14
Occasional pain since operation	10
As much pain as before operation	0
Parent considered operation to have helped child	23
Parent did not consider operation to have helped child	1

Review of the symptoms and signs in this series reveals that in children the most reliable criteria for establishing the diagnosis of appendicitis are, in order of importance, abdominal pain, vomiting, low-grade fever, leukocytosis, increased spasm of the abdominal musculature on the affected side and localized tenderness. Diminished or absent peristalsis and extreme rectal tenderness or rectal mass are significant findings.

This series suggests that in carefully selected patients with a history of recurrent abdominal pain, "interval appendectomy" is likely to yield a favorable result.

From a comparison of mortality figures of previous years in this hospital it is our unavoidable conclusion that the antibiotics have helped materially in reducing the mortality rate of appendicitis.

SUMMARY AND CONCLUSIONS

In a survey of all children under thirteen years of age subjected to appendectomy at the Boston City Hospital from 1950 to 1953, 74.07 per cent had some form of appendiceal disease. The negative diagnostic error rate was thus 25.9, and the positive rate 4 per cent. The over-all mortality was 0.24 per cent, the one fatal case occurring in a child given a spinal anesthetic.

The symptoms and signs of appendicitis are reviewed.

Among 45 patients undergoing "interval appendectomy" 20 of the 24 subsequently located were reported improved by their parents.

Although attempts must be made to lower the rate of diagnostic error of this series caution should be exercised lest the rate of positive diagnostic error, and thereby the mortality rate, be increased.

REFERENCES

1. Ward-McQuaid, J. M. Acute non-specific mesenteric adenitis: incidence and prognosis in children. *Lancet* **2**:524-527, 1951.
2. Hawley, P. R. Ideals and ethics of medicine. *Bull. Am. Coll. Surgeons* **38**:133-137, 1953.
3. Gross, R. E. *The Surgery of Infancy and Childhood: Its principles and techniques.* 1000 pp. Philadelphia: Saunders, 1953. P. 44.
4. McLanahan, S. Further reductions in mortality in acute appendicitis in children. *Ann. Surg.* **131**:853-864, 1950.

LINEAR X-RAY SHADOWS IN ACQUIRED PULMONARY HEMOSIDEROSIS AND CONGESTION*

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BOSTON

FAINT horizontal linear shadows are often observed in the lower lateral fields of the lung on roentgenograms of patients suffering from either acute or chronic recurrent pulmonary congestion, particularly in severe mitral stenosis. We have seen identical lines in pulmonary hemosiderosis in the absence of acute pulmonary congestion. This observation has not previously been recorded, either in the original descriptions of the latter condition by Rosenhagen[1] and Zdansky[2] or in the more recent comprehensive reviews by Scott et al.[3] and Pendergrass and his co-workers.[4]

These linear shadows are usually best seen just above the costophrenic angle along the lateral chest wall, on the routine posteroanterior view. However, at times they are depicted to better advantage along the lateroposterior chest wall, on the oblique roentgenogram. They are arranged perpendicularly to the lateral chest wall and may be visible for as high as 8 to 10 cm. above the costodiaphragmatic angle. They are delicate, ranging from mere visibility to a width of 0.1 to 0.2 cm. They usually do not extend into the lung fields for more than 1 to 3 cm. They are spaced 0.5 to 1.0 cm. apart.

The nature of these linear shadows has not been determined. Some writers regard them as small areas of atelectasis, and others as bands of interstitial fibrosis. Kerley[5] considers them to be caused by engorged lymphatics or interstitial edema.

These linear shadows may be either persistent or fleeting.

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Persistent Shadows

For many years our search for the anatomic substratum of these lines had been unsuccessful. By comparing their arrangement with the normal lung architecture, we have long suspected these lines to correspond to interlobular septums made prominent by some undetermined mechanism. Recently, we had the good fortune to study holoptic microtome sections of several different lungs kindly furnished us by Dr. J. Gough,[6] of Cardiff, Wales. Sectioned at 400-micron thickness by a special method developed by him in collaboration with I. E. Wentworth, these large slices comprised the whole lung and thus provided unparalleled insight into the pulmonary topography. Gough has been mainly interested in anthracotic pneumoconiosis observed in Welsh coal miners. In preparations of slight and moderate anthracosis of the lungs, the coal pigment deposited along and within the interlobular septums made the pattern of the septums stand out quite prominently. Figure 1, a photograph

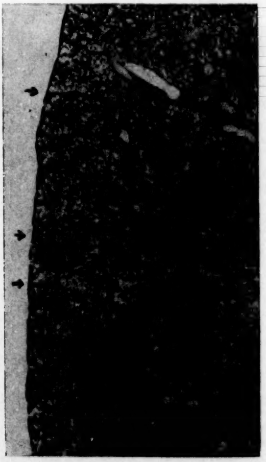

Figure 1. *Photograph of a Lung Specimen (Natural Size) from a Patient with Moderate Anthracosis.*
The coal pigment is arranged mainly along the interlobular septums (black lines perpendicular to the pleural surface of the lung, some of them marked by arrows).

in natural size of a section of such a specimen, shows a marked similarity in arrangement between these coal-impregnated interlobular septums and the horizontal lines in question on our roentgenograms. To avoid misunderstandings it is emphasized that coal deposits of this kind, being radiotranslucent and producing little or no fibrosis, are not necessarily visible on a roentgenogram.

One of Dr. Gough's specimens was from a patient with long-standing mitral stenosis showing brown induration of the lung and recent pulmonary embolism with infarct formation. A slice of this lung, treated with Prussian-blue stain for the demonstration of iron pigment, showed dark-blue lines against a background of diffuse, lighter blue. The over-all arrangement, spacing, width and length of these blue lines followed

Figure 2. *Photograph of the Lung from a Patient with Mitral Stenosis (Prussian-Blue Stain, Natural Size), Showing the Main Interlobar Fissure.*
To the left is the lingula, showing widened interlobular septums with hemosiderin on each side. In the lower lobe, on the right, are dark lines caused by hemosiderin deposits (arrows).

the pattern of the interlobular septums (Fig. 2). Preferential accumulation of iron pigment along interlobular septums in the hemosiderotic lung was described and illustrated by Ceelen[7] in 1931 in his Figures 3*a* and 5.

Histologic Observations

In addition to 4 cases in which these lines had been observed on roentgenograms during life, the routine microscopical slides of the lungs in 6 cases with autopsy diagnosis of chronic passive congestion were reviewed. Thirty-four slides (average thickness, 8 microns) ranging from 2 to 7 slides per autopsy were suitable for analysis of the localization of hemosiderin in the lobular architecture of the lung. In the majority of the cases hemosiderin pigment appeared accentuated in a linear fashion, in relation to interlobular septums under low-power microscope scanning. This accentuation was usually less obvious than that in Dr. Gough's much thicker sections. In several of these lungs hemosiderin had also become concentrated about bronchoarterial trunks, but truncal accentuation without simultaneous septal concentration was rare. Hemosiderin-laden macrophages were also commonly present throughout the lung lobules. Thus, diffuse intralobular scattering of hemosiderin and accentuation of interlobular septums or bronchoarterial trunks did not necessarily exclude each other in the same slide or, in the same patient, in different slides. However, intense hemosiderosis distributed diffusely throughout

the lobules obscured the linear accentuation of hemosiderin deposits.

Hemosiderin macrophage accentuation in relation to interlobular septums consisted of two components: the bulk of the pigment was in air spaces abutting on the septums and trunks, and only relatively little was found within the corresponding stroma. Instead of flanking the septums on both sides the marginal hemosiderin was often on one side. Occasionally, such marginal flanking of hemosiderin was on alternate sides once or several times as one surveyed the length of a given interlobular septum.

The recognition of the linear arrangement of accumulated hemosiderin, even in sections as thin as 8 microns, is thus conditioned mainly by three factors: the intraseptal deposition of hemosiderin (occasionally hemosiderin was deposited on a nucleus of anthracotic pigment, suggesting that the intrapulmonary disposition of these two pigments follows a similar course); the paraseptal accumulation of hemosiderin macrophages; and the intensity difference of the septal-paraseptal bands on the one hand and the hemosiderin deposition in the lung lobules, as a whole, on the other.

The accumulated hemosiderin macrophages, both inside and outside the interlobular septums or bronchoarterial trunks, rarely produced any fibrosis. Anatomically, there is probably no preference of linear hemosiderin accentuation for the lower lobes, an observation also confirmed by Dr. Gough's specimen.

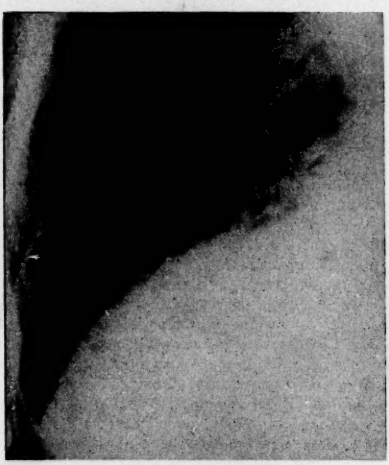

FIGURE 3. *Roentgenogram in Case 1. The light horizontal lines in the lateral portion are clearly visible.*

One of the slides showed paraseptal hemosiderin lines as well as fresh hemorrhages, which failed to exhibit any paraseptal preference. From this and other considerations it is believed that the accentuated truncal and septal distribution of hemosiderin is a secondary phenomenon of preferential accumulation of hemosiderin macrophages and clearing of the other, more centrolobular air spaces through migration or possibly expectoration. This interpretation conforms with Magarey's[8] observations in experimental pulmonary hemosiderosis.

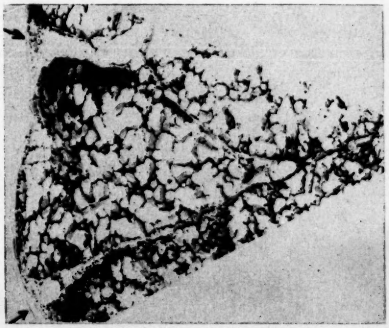

FIGURE 4. *Low-Power Photomicrograph of the Right Lower Lobe in Case 1 (Prussian-Blue Stain, Photographed through an Orange Filter).*

There is preferential concentration of hemosiderin alongside and within two interlobular septums, which thereby come to stand out prominently (arrows). The intraseptal, but not the paraseptal, hemosiderin is commonly encrusted on anthracotic centers. There is little hemosiderin in the more central portions of the lobules.

CASE 1 (B. I. H. M41698). A 51-year-old man, known to have had rheumatic heart disease for 17 years, with mitral stenosis and aortic insufficiency, atrial fibrillation and bacterial endocarditis, had been followed by us for 3 years with repeated episodes of congestive heart failure. Delicate horizontal linear shadows in the lower lateral lung fields were visible even at times of fair compensation. Figure 3 presents the right-lower-lung field of a chest roentgenogram obtained 3 weeks before death. Autopsy confirmed the clinical diagnosis and revealed pulmonary hemosiderosis of mild to moderate degree. Figure 4, a low-power view of a microscopical section from the lateral portion of the right lower lobe, shows iron pigment arranged in a linear fashion along 2 interlobular septums approximately perpendicular to the pleural surface of the lung.

Iron with an atomic weight of 56 is known to absorb roentgen rays sufficiently to cast flecky shadows if accumulated in nodular fashion. If deposited selectively in a plane fashion and met tangentially by the roentgen beam, it will cast a linear shadow. In the superficial (that is, the subpleural) layers of the lung, many interlobular septums are perpendicular to the lateral chest wall, and, with the subject in erect position, many septums will be in a horizontal plane. The horizontal beam, such as that used for the routine chest roentgenogram, hits these septums in a parallel or tangential fashion. These anatomic and physical facts, combined with the accentuated ac-

cumulation of hemosiderin along the interlobular septums, leave little doubt that the horizontal linear shadows are cast by iron-coated interlobular septums. Although, in the histologic sections, there is no restriction of iron deposition to the dependent parts of the lung, the roentgenologic and anatomic considerations presented above adequately explain why these lines are best recognized in the lower lateral portions of the lung fields.

We have seen identical linear shadows in some cases that presented the full appearance of acquired pulmonary hemosiderosis with extensive nodularity throughout both lung fields. Even more often, however, we have observed them in lungs with lesser degrees of iron—pigment deposition—that is, without such disseminated nodularity.

Transient Shadows

Although the persistent horizontal linear shadows can be verified in the pathological specimen the identification of linear shadows of fleeting character is more difficult.

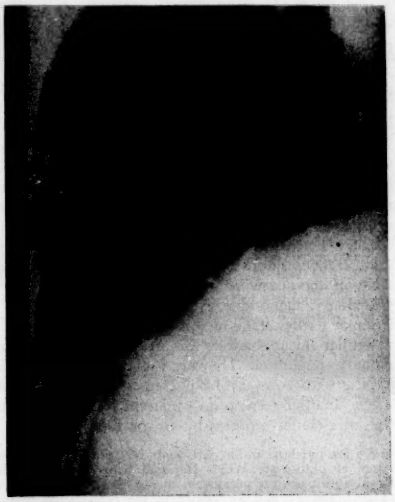

Figure 5. *Section of the Right Lower Lobe in Case 2.*

Case 2 (B.I.H. M35162). A 58-year-old woman with rheumatic mitral stenosis had been under observation for several years. X-ray examination of the right-lower-lung field of the chest in August, 1951, showed no gross abnormality (Fig. 5). She was readmitted to the hospital for congestive heart failure on October 31, 1952. There was roentgenologic evidence of severe pulmonary congestion. In addition horizontal linear shadows in the lateral portions of both lower-lung fields were observed (Fig. 6). Treated with bed rest, digitoxin, aminophylline and a low-salt diet, the patient improved within a few days. Four days later the pulmonary congestion had subsided, and the linear shadows had receded to questionable visibility (Fig. 7).

The horizontal linear shadows in Case 2 are characterized by their fleeting nature. Their striking roentgenographic and morphologic similarity to the lines seen in hemosiderosis suggests that they, too, are cast by interlobular septums. Because they are transient, however, a fugitive anatomic substratum might be expected. Since they appear with the clinical onset of pulmonary congestion and regress, or vanish completely, simultaneously with clinical improvement of the patient, we conclude that the interlobular septums have become widened and thus visible radiologically on account of absorption of edema fluid.* Anatomically, Parker and Weiss[10] described and illustrated such edematous widening of the interlobular septums in mitral stenosis. It is of particular significance that this occurred without concomitant intra-alveolar edema of the adjacent lung tissue.

Figure 6. *Film of the Chest in Case 2 Taken on October 30, 1952, When the Patient Was in Congestive Heart Failure (Note the White Horizontal Lines).*

Recently, we were impressed by the observation of a patient suffering from mitral stenosis. Horizontal lines that had been present for a considerable time disappeared after a successful valvuloplasty, and at the same time the basic radiolucency of the lung fields increased.

As exemplified by Case 2 edema of the interlobular septums seems the best explanation of the transient

*In 1949 Kerley[9] made the following comment: "I suppose this rapid reversal to normal can only lead to an interpretation of these striae as interstitial edema."

nature of the linear shadows. Yet hemosiderin, once present, may also disappear, however slowly, either by expectoration if intra-alveolar or, among other possibilities, by migratory displacement if interstitial. Thus, in the case of valvuloplasty referred to above,

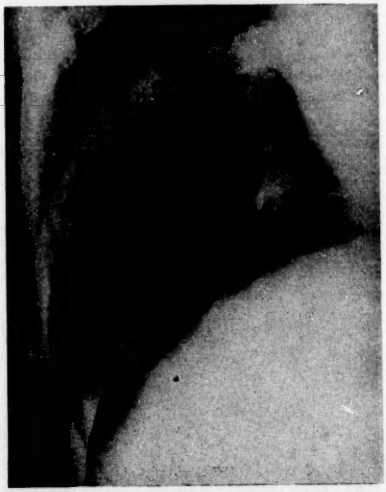

FIGURE 7. *Film of the Chest in Case 2 after Recovery. The horizontal lines have almost disappeared.*

the disappearance of the linear shadows may have been due not only to diminution of chronic interstitial edema but also to dissipation of hemosiderin once the element of vascular stasis, responsible for further hemorrhages and hemosiderin production, had been corrected.

DISCUSSION

The similarity of the general arrangement of the horizontal lines observed in the roentgenograms to the structural arrangement of the interlobular septums suggested close correspondence. A certain degree of preferential concentration of iron pigment alongside and within the interlobular septums in the hemosiderotic lung provided a substrate that could be confirmed in the pathological specimen. By analogy, similar transient linear shadows were interpreted, in cases of pulmonary congestion, as edematous interlobular septums. We have observed similar shadows in occasional cases of pneumoconiosis and diffuse pulmonary fibrosis, in which it is assumed that the interlobular septums become visible by fibrous thickening.

These short horizontal lines, once their nature is recognized, can hardly be mistaken for anything else. Plate-shaped areas of atelectasis are usually much thicker and extend more deeply into the lung. They are hardly spaced in this regular fashion of pulmonary lobules even if they are multiple. Intrapulmonary scars of infarcts or of interstitial extensions of pleurisy are coarser and mostly accompanied by visible pleural thickening.

We do not think that one can distinguish, on a single roentgenogram, between lines caused by hemosiderin deposits and those caused by edema of the interlobular septums. The whole clinicoroentgenologic setting, however, and persistent versus fleeting behavior, as observed over a period of time, will usually allow for final distinction.

The arrangement of edema fluid in the lung is subject to factors largely unknown in the individual case. In a given case, however, the increase and decrease of these edema lines have been found to reflect very well the change in the degree of moisture in the lung parenchyma.

SUMMARY AND CONCLUSIONS

Thin horizontal linear shadows occur in the lateral lower-lung field of chest roentgenograms of patients with acute or long-standing recurrent pulmonary congestion, mainly in patients with mitral-valve disease. These lines are perpendicular to the lateral chest wall, parallel to each other and spaced 0.5 to 1.0 cm. apart. They extend into the lung field for 1.0 to 3.0 cm. They may be persistent or transient.

The persistent lines are shown to be cast by hemosiderin preferentially appearing alongside and within interlobular septums. In patients with chronic pulmonary congestion these lines may or may not be accompanied by other roentgenologic evidence of pulmonary hemosiderosis. Indeed, linear shadows are more frequently observed than the generalized nodularity of the classic picture of far-advanced acquired pulmonary hemosiderosis and apparently reveal a lesser or earlier stage of this condition.

Similar linear shadows are often seen in acute pulmonary congestion. They are fugitive and mostly disappear with recovery from congestive heart failure. Their anatomic substrate apparently is widening of the interlobular septums by edema fluid.

We are indebted to Dr. J. Gough, of Cardiff, Wales, professor of pathology, Welsh National School of Medicine, Royal Infirmary, for permission to use his special specimens (Fig. 1 and 2) and for advice in the preparation of this study.

REFERENCES

1. Rosenhagen, H. Über einige Beziehungen zwischen histologischen Veränderungen und Röntgenbild bei der chronischen Stauungslunge. *Fortschr. a.d. Geb. d. Röntgenstrahlen* **38**:353-359, 1928.
2. Zdansky, E. Beiträge zur Kenntnis der kardialen Lungenstauung auf Grund röntgenologischer, klinischer und anatomischer Untersuchungen. *Wien Arch. f. inn. Med.* **18**:461-486, 1929.
3. Scott, L. D. W., Park, S. D. S., and Lendrum, A. C. Clinical, radiological and pathological aspects of pulmonary haemosiderosis. *Brit. J. Radiol.* **20**:100-107, 1947.
4. Pendergrass, E. P., Lame, E. L., and Ostrum, H. W. Hemosiderosis of lung due to mitral disease: report of six cases simulating pneumoconiosis. *Am. J. Roentgenol.* **61**:443-456, 1949.
5. Kerley, P. In *A Text-Book of X-Ray Diagnosis*. Edited by S. C. Shanks and P. Kerley. Vol. 2. 702 pp. Second edition. Philadelphia: Saunders, 1951. P. 68.

6. Gough, J., and Wentworth, J. E. Use of thin sections of entire organs in morbid anatomical studies. *J. Roy. Microscop. Soc.* **69**: 231-235, 1949.
7. Ceelen, W. Die Kreislaufstörungen der Lunge. In Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie.* 701 pp. Vol. 3. Part 3. Berlin: Springer, 1931. Pp. 1-163.
8. Magarey, F. R. Experimental pulmonary haemosiderosis. *J. Path. & Bact.* **63**:729-754, 1951.
9. Kerley, P. Idiopathic pulmonary fibrosis. Presented at the New England Roentgen-Ray Society, Boston, February 18, 1949.
10. Parker, F., Jr., and Weiss, S. Nature and significance of structural changes in lungs in mitral stenosis. *Am. J. Path.* **12**:573-598, 1936.

MALNUTRITION OF THE NEWBORN SECONDARY TO PLACENTAL ABNORMALITIES

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SINCE statements of neither the day of conception nor the date of the last menstruation are usually reliable, most physicians consider an infant weighing less than 2.5 kg. (5½ pounds) to be premature. The diagnosis of "prematurity by weight only" is frequently made when information indicates a full-term pregnancy.

Some of these infants regarded as premature solely because of their weight can be assumed to be hereditarily small. Others are malnourished.

Recently, 3 such undernourished infants, whose poor nutritional status presumably was caused by abnormalities of the placenta, came to my attention. The clinical course was similar in all and differed considerably from the usual course in the newborn period of the premature infant.

CASE REPORTS

CASE 1. G. Ch., an infant girl, was born at full term after an uneventful pregnancy. Labor lasted 9 hours, and delivery was by low forceps. The birth weight was 1.8 kg., and the crown-heel length was 48.3 cm. The parents were of average stature. On physical examination the infant showed scant subcutaneous tissue, had a scaphoid abdomen and was best described as "emaciated." The baby was active; her color was good, and there was no evidence of infection or anomalies. The cry was good, and the sucking reflex normal.

The placenta was small, measuring 16 by 13 by 2 cm. It looked grossly abnormal to the obstetrician and revealed large foci of old infarction microscopically. The umbilical cord demonstrated thickening of the arterial walls and marked narrowing of the arterial lumens.

The baby gained weight rapidly on an evaporated-milk formula with 7 per cent carbohydrate added. At 2 weeks she weighed 2.2 kg. At 4 months of age she weighed 5.6 kg. and was 58.4 cm. tall; she was normally active and reached for moving objects. She sat alone at 7 months and walked with support at 11 months. At 1 year she weighed 9.4 kg. and was 71.1 cm. tall (Table 1).

CASE 2. D. W. L., a baby boy, was delivered by low forceps after an uncomplicated pregnancy and 7 hours of labor, 2 weeks after the expected date of confinement. The birth weight was 2.2 kg. (Table 1), and the length at birth was 53.3 cm. The parents were tall and heavy set. At birth the infant was intensely cyanotic, breathed feebly in spite of vigorous resuscitation and appeared almost lifeless. He was described as "marasmic." The skin was very dry and peeling and had a yellow tint. The ribs were prominent, and practically no subcutaneous tissue was present. His condition was so precarious and he was so emaciated that the obstetrician was convinced that he could not survive for more than a brief period after delivery. There was no evidence of infection and no heart murmurs or other anomalies.

The placenta was friable and foul smelling. The umbilical cord was stiff and yellow. On microscopical examination the placenta showed a large area of hyalinization. The umbilical arteries were thick walled, and the intima demonstrated hyperplasia and fibrosis without inflammation.

After 48 hours of great respiratory difficulty in spite of oxygen therapy the patient showed spectacular and unexpected improvement on an evaporated-milk formula with 7 per cent carbohydrate added. At 6 weeks he weighed 3.6 kg. and at 4 months, when he was 44.8 cm. long, 7.2 kg. He turned over at 4½ months and sat alone at 5 months. At 1 year he weighed 11.3 kg., was 73.7 cm. tall, was able to pull himself into the standing position and walked with little support.

TABLE 1. *Data in 3 Infants with Malnutrition of the Newborn.*

CASE NO.	SEX	BIRTH WEIGHT	TIME OF DELIVERY	PERIOD BEFORE BIRTH WEIGHT REGAINED	WEIGHT AT 2 WK.	PERIOD BEFORE DISCHARGE FROM HOSPITAL*	PERIOD BEFORE WEIGHT DOUBLED	WEIGHT AT 1 YR.
		kg.		*days*	*kg.*	*days*	*wk.*	*kg.*
1	F	1.8	At term	(Birth weight lowest weight)	2.2	20	Less than 10	9.4
2	M	2.2	2 wk. beyond term	6	2.5	15	Less than 10	11.3
3	F	1.6	At term	4	2.1	21	Less than 7	—

*When infant weighed more than 2.5 kg.

*Pediatrician, Burbank Hospital; clinical associate in children's medicine, Massachusetts General Hospital.

CASE 3. N. C., a baby girl, was delivered at full term after 48 hours of labor by breech extraction; pregnancy had been uneventful. The parents were of average stature. The birth weight was 1.6 kg. (Table 1), and the crown-heel length was 48.3 cm. At birth the baby was cyanotic, and resuscitation was difficult. On physical examination she was very thin, with prominent ribs and sternum. There was no evidence of infection, and no anomalies were noticed. The cry was feeble. The sucking and Moro reflexes were normal. After several hours in the incubator with oxygen and high humidity, her color improved. On the 3d day she began to eat voraciously and gained weight rapidly on an evaporated-milk formula with 7 per cent carbohydrate. She was discharged after only 3 weeks in the hospital weighing 2.6 kg.

The placenta was described by the obstetrician as being unusually small — "about the size of an orange." Unfortunately, the placenta was not submitted for pathological study.

At 8 weeks the patient weighed 3.7 kg. At the last examination, when she was 3 months old, the weight was 5.1 kg., and the length 56 cm. She had started to reach for dangling objects, laughed out loud and was very alert.

DISCUSSION

Since all 3 infants weighed less than 2.5 kg. and were delivered at term they can be classified as "premature by weight only." The parents of the infants were of average build. All 3 placentas were grossly abnormal. The 2 placentas examined microscopically showed proliferative endarteritis of the umbilical arteries and large areas of hyalinization.

According to Hess[1] the intervals presented in Table 2 can be expected before premature infants regain their birth weight.

The percentage loss of weight in premature infants is, on the average, relatively greater than that of full-term babies, and they therefore take a longer time to regain the birth weight. The infants described above, on the basis of birth weight, might have been expected to regain that weight in twelve to fourteen days. However, 1 lost no weight at all, and the other 2 regained the birth weight in four and six days (Fig. 1). At two weeks 1 baby had gained 255 gm., and the other 2 infants 450 gm. (about 28 per cent of the birth weight). It took less than two and a half months for the birth weights to double (Table 1).

Clifford[2] states that North American premature boys attain the weight of their full-term brothers at four years and the Woodbury norms at three years. The girls approximate the Woodbury norms at nine to twelve months. However, the 3 infants described above were developmentally and physically indistinguishable from term infants when examined at four and six months of age (Fig. 2).

It is believed that these infants were undernourished and not premature. This malnutrition was presumably due to an abnormal placenta, which prevented proper nutrition of the fetus. The infants gained remarkably as soon as an adequate caloric intake was included in the formulas.

These case studies emphasize the necessity of examining the placenta for abnormalities. Actually, little is known about diseases of the placenta in relation to the nutrition of the newborn. In the commonly used textbooks of pediatrics no discussion can be found on this topic. Potter[3] states, "If a disturbance causes cessation of the placental growth, the fetal growth is interrupted because of an inadequate source of food material and oxygen."

Rumbolz and McGoogan[4] recently described 20 cases of "placental insufficiency" resulting in small, undernourished infants. Nineteen of the placentas showed infarcts of varying sizes; the placentas that were weighed were all less than the normal weight of 500 gm. The authors pointed out that clinically the presence of a full-term small infant and "placental insufficiency" may be suspected if the uterus fails to enlarge during the last trimester of pregnancy.

Clifford[5] recently reported that infants with the "postmaturity syndrome" show a yellow-stained ver-

TABLE 2. *Expected Intervals before Premature Infants Regain Birth Weight.*

BIRTH WEIGHT gm.	INTERVAL BEFORE BIRTH WEIGHT REGAINED days
1000 — 1500	18.6
1500 — 2000	14.7
2000 — 2500	11.8
2500 — 3000	12

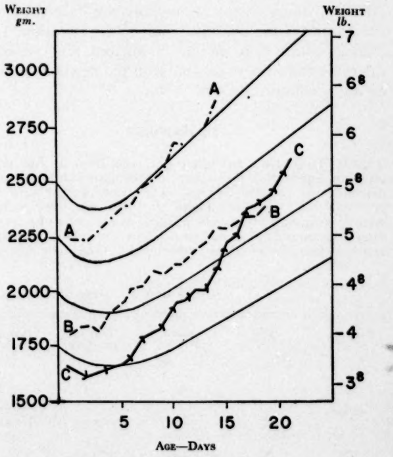

FIGURE 1. *Weight Gain of 3 Infants with Malnutrition of the Newborn Secondary to Placental Abnormalities. The weight gain in the nursery is plotted against the expected norm for premature infants. It can be seen that these undernourished babies gained much faster than one would expect of ordinary premature infants.*

nix, have a peeling skin, are alert and gain fast, if they survive. None of his premature infants, however, had a birth weight under 2.5 kg.[6] though it is emphasized that they are poorly nourished. One of the 3 infants described above was postmature by two weeks; the other 2 were delivered at term. It is possible that these babies were similar to the postmature infants discussed by Clifford.

Since the gestational age is admittedly inaccurate, it seems important to stress the pathologic changes in the placenta and correlate them with the status of the newborn. There are probably a variety of etiologic factors that cause pathologic changes in the placenta, which in turn result in malnourished infants. Postmaturity may be one of these factors.

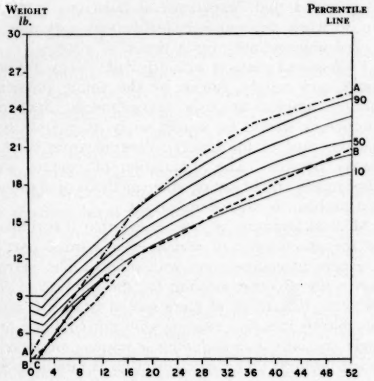

FIGURE 2. *Weight Gain of 3 Infants with Malnutrition of the Newborn during the First Year of Life. It will be noted that these infants gained fast and reached values for normal infants by three or four months.*

A diagnosis of abnormalities of the placenta or of a malnourished infant can be made only after delivery by a careful examination of the placenta and the infant. It is necessary for obstetricians, pediatricians and pathologists alike to pay more attention to this organ. Only then will some of these malnourished infants not be classified as premature.

SUMMARY

Three infants are described who at birth were malnourished, presumably because of an abnormal placenta. Although their birth weight was less than 2.5 kg. (5½ pounds) they were not premature. Their postnatal course differed from that of premature infants in that they regained their birth weight more rapidly, doubled their weight in less than ten weeks and were indistinguishable from full-term infants at the age of four and six months.

These malnourished infants are discussed in relation to Clifford's "postmaturity syndrome," and the view is advanced that postmaturity may be one of several etiologic factors that may produce a malnourished infant through an abnormal placenta.

A plea is made to examine the placenta after delivery so that more can be learned about the relation of the placenta to the nutritional status of the newborn.

I am indebted to Dr. H. Judd Sparling for his pathological examination of the placentas and for his helpful suggestions in the preparation of this paper, and to Dr. Stewart H. Clifford for advice and editorial suggestions.

Since this paper was submitted for publication a detailed discussion of this subject has been presented by Clifford.[7]

REFERENCES

1. Hess, J. H. Premature infant. In *Brennemann's Practice of Pediatrics*. Vol. 1. Chap. 43. Hagerstown: Prior, 1942. P. 5.
2. Clifford, S. H. Premature infants. In *The Child In Health and Disease*. Edited by C. G. Grulee and R. C. Eley. 1255 pp. Second edition. Baltimore: Williams and Wilkins, 1952. P. 163.
3. Potter, E. L. *Pathology of the Fetus and the Newborn*. 574 pp. Chicago: Year Book Publishers, 1952. P. 27.
4. Rumbolz, W. L., and McGoogan, L. S. Placental insufficiency and small undernourished full-term infant. *Obst. & Gynec.* **1**:294-301, 1953.
5. Clifford, S. H. Postmaturity clinical syndrome and pathologic findings. *Am. J. Dis. Child.* **86**:319, 1953.
6. *Idem*. Personal communication.
7. *Idem*. Postmaturity with placental dysfunction: clinical syndrome and pathologic findings. *J. Pediat.* **44**:1-13, 1954.

SPECIAL ARTICLE

MEDICAL ORGANIZATION*

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MEDICINE is not static. Neither can the practitioner of medicine remain static. However well prepared he may be on entering the profession, he will either advance or retreat from that point. If he is to grow he must constantly strive to improve his knowledge of the science of medicine, broaden and consolidate his experience and perfect his technic in the art of its practice. Medicine is also a social force and is played upon by other social forces, which will, to a high degree, determine the environment in which medicine is practiced and will stimulate or retard its progress. Social and economic factors may affect medical education and research and the production, distribution and cost of medical care. The doctor's activities should therefore include participation in the social and economic fields of medicine.

As his primary concern the physician must, of course, continue throughout life the program of medical education begun in medical school. Since the frontiers of medical knowledge are constantly changing, whatever degree of education and training he may have on entering practice is only a basis for further advance in knowledge and skill.

Medical education at the local level may be continued by study of one's own cases, by reading and by contacts with fellow physicians in the local medical society and at hospital staff conferences. The most effective means of advancing one's own knowledge is in teaching others, even though in a small way. Hospital appointments may afford this advantage. At the state and national level special courses sponsored by medical societies, hospitals and medical schools offer unlimited opportunities.

RECORDING OF CLINICAL EXPERIENCE

Experience gained is of little value unless recorded and compared with the experience of others. Records are necessary, not only for the benefit of having a continuous story of a patient's troubles over a given period but also to preserve one's own intellectual honesty. Without records, therapeutic triumphs become magnified, and the unpleasant facts of failures are dimmed or forgotten. Nothing is more stimulating, or at times perhaps more humiliating, than, on review of a case, to have recourse to a record of years before that indicates how correctly the patient's problem was evaluated at the time of the previous examination. Hippocrates may have had this in mind when he observed that "experience is fallacious." This is not so when experience is fortified by carefully recorded observations over a period of years.

Professional contacts with other physicians are necessary and can be gained by the young physician through hospital or clinic appointments. Such appointments should be sought early no matter how low the rung of the ladder. Progress from there is always possible. The stimulation of contact with other minds and of noting other methods of approach to a problem is always important.

Medical literature is so extensive that it is difficult for the practitioner to review even a small part of it, except in co-operation with others. The journal club is an effective medium for the solution of this problem. Regardless of one's special field, it is often valuable to join in a reading club not confined to a single specialty but including a number of men of varied interests. The specialist who is familiar with only his own particular branch of medicine is greatly handicapped. He should, at least, know the capabilities of the general practitioner and of the specialists in the various fields, and what can be offered his patient by each of them. The reading club affords an opportunity of hearing an evaluation of many articles covering the different phases of medicine. One can then select the papers that appear to have particular value for further detailed study. After having had experience in the general type of journal club, one may later choose a club limited to a special field of medicine.

With this background of recording of clinical findings, based on the study of one's own patients and of those encountered in clinics, together with a knowledge of current medical literature, one is prepared to take part in discussions of scientific subjects in the medical-society and staff conferences. Exposure to the criticism and comments of others emphasizes the necessity of being able to fortify one's opinions by fact and helps develop some facility in speaking and in writing. From there on opportunity broadens, and progress is limited only by one's devotion to the art and science of medicine, and willingness to work. Progress in postgraduate education can continue throughout life, and can move from the local to the state and to the national level.

*Adapted from a chapter with the same title in the forthcoming book, *The Physician, His Practice and His Business*, by permission of the publisher, Little, Brown and Company, Boston.

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Specialty Boards

Those who enter the practice of medicine come with different equipments. They may have progressed through a full residency and completed the formal training required by the board of the specialty of their choice. Others may have had less training, down to a single year of internship. In some cases this has been by choice, and in others it has been a matter of necessity. Many capable students find themselves unable, even if they so desire, to complete the formal training required for admission to the examinations of one of the specialty boards. Fortunately, in this country, the way remains open for them to enter practice and qualify for board examinations later. The requirements of the several boards vary. These requirements are set forth each year in the internship and residency number of the *Journal of the American Medical Association*. The student and the young physician should review these requirements carefully so that they can plan the courses that they desire to pursue. Whatever one may think of the present rigid requirements of certain boards, they do, to a considerable degree, control the destiny of the individual physician.

There are at present 19 specialty boards, not including certain subspecialties certified by some of the specialty boards. The Advisory Board for Medical Specialties was organized in 1933 and 1934. This board is made up of 2 members from each of the approved medical specialty boards and 2 from 4 other organizations with a legitimate interest in the education, examination and certification of medical specialists. These 4 are the Association of American Medical Colleges, the American Hospital Association, the Federation of State Medical Boards and the National Board of Medical Examiners. Before the organization of this advisory board certain specialty boards were already in existence, and there was nothing to prevent any medical group from establishing a board in any particular field. The 19 specialty examining and certifying boards are set up under the Council on Medical Education and Hospitals of the American Medical Association, and the Advisory Board for Medical Specialties.

The purpose of the examining boards in the specialties is to determine the competency in a certain field of candidates who present themselves for certification. These boards are also concerned with the development and evaluation of training facilities. They advise physicians regarding a proper course of study, training and preparation for examination by the boards. Certification does not confer any special or legal qualification. It does not interfere in any way to limit the practice of a nonboard member who conforms to the law of his state, and who considers himself competent to practice in a certain field.

Certain general qualifications are required by all boards, such as citizenship, moral and ethical standards and active membership in local and state societies. The last requirement is waived for physicians in the federal medical services and, under certain exceptional circumstances, for others. Each of the 19 boards has its own particular requirements in terms of education, training and experience. Information about the requirements of any specialty board may be obtained from the Advisory Board for Medical Specialties.

The medical student, as early as possible in his career, should become familiar with the requirements of the several boards, so as to plan his future activities accordingly. It is not necessary and, indeed, not always desirable for him to pursue his postgraduate studies through a full residency course and thus to meet the formal training requirements of the boards. There is much to be said for interrupting training after the second graduate year and thus gaining experience in the practice of medicine before formal training has been completed. Knowledge, without the wisdom acquired from experience in the responsibility of actual practice, may at times be a detriment. Certainly, this experience in practice is of great value to the student who resumes his formal training after an interlude spent in the practice of medicine. Provision made by the Board of Internal Medicine, whereby these additional years in practice and special study may be substituted for certain years of more formal training, has much to commend it.

General practice must always be the sound basis of good medical care in this country. At present more than two thirds of the physicians actively engaged in the practice of medicine are general practitioners. They are sharing to an increased extent in the available facilities for postgraduate training. Many teaching hospitals are offering two-year mixed internships, designed particularly for those who plan to enter general practice. Hospitals are also establishing sections on general practice on both an inpatient and an outpatient basis. The Academy of General Practice requires of its members a certain number of hours of postgraduate experience each year.

The present military situation has posed a problem for the military, the teaching hospitals and the student alike. A young physician, after completing his first year of internship, is liable to be called for a two-year tour of duty with the armed forces. If he is not called he can be deferred for a six-month period only, but after this he may or may not be again deferred. This presents the hospitals with an unstable group in resident training, and keeps the student in a state of jeopardy. This program, which supplies the armed forces with a large group of men with only a year's training, leaves a dearth of those needed to fill the gap between the ward officer and the chief of service. The problem, of course, does not present itself to those who have already discharged their military obligation, but this group is decreasing rapidly.

Societies and Associations

Men in almost every walk of life join organizations in which they have a common interest or a common objective. Their objectives may be altruistic or selfish and may often be a mixture of both. Joining has become a part of the pattern of American life. Medicine is no exception. National, state and local medical societies abound. No physician can be insensible of their impact on medicine, nor can he stand apart from the associations that will further his purposes as a good physician. If he is to continue to advance in medical knowledge and if he is to discharge his full duty to society by aiding in the solution of the problems of medicine, he must join with men of like interests and similar purposes.

The county medical society, which is the basic and probably the most important unit in medical organization, should be one of the most useful groups in any community. Through the county society the physician becomes acquainted with his fellow practitioners and should become aware of the broad general medical and social problems in his immediate area. If he is to discharge his proper function as a physician, he cannot confine his interests and activities to the field of professional activities alone. From the local medical society he should broaden out into activities in other community groups — religious, civic and welfare.

He should early seek hospital or clinic staff appointments and devote a suitable part of his time to nonremunerative activities in the field of medicine. Association with the local medical society should not be limited to joining with the purpose of establishing his standing in medicine. He should attend the meetings, listen to and, when informed, take part in the discussion. In his early years, when not too much pressed for time, he should form a habit of participation in the society work that will persist in later years, even though other demands crowd upon him. The good local medical society is a focal point from which the total health needs of a community can be observed, studied and evaluated. From the society should come the stimulus to the improvement of preventive services, hospital facilities and measures for the extension of good medical care to all the people of the community.

The next step in the organizational phase of medicine is the state society. Here, the broader aspects of medicine come into view as they affect the state and often the surrounding areas. Each county society, at an annual meeting, elects representatives to the state society's house of delegates or council. Whereas the total membership in a local society formulates the policy and takes action on matters brought before it the house of delegates of the state society may transact its business only at its annual meeting. During the interval between meetings of the house of delegates the affairs of the society are controlled or managed by a board of trustees, or some other small group elected by the delegates. The state societies and associations also elect delegates to the House of Delegates of the American Medical Association. Each state is entitled to 1 representative in the national House of Delegates for each 1000 members, or fraction thereof, of the society who are active members of the American Medical Association.

The American Medical Association is made up of 53 state and territorial organizations. The House of Delegates comprises representatives from the various states and territories, together with representatives of each of the scientific sections of the Association, and one from each of the five major divisions of the federal medical services. The House of Delegates of the American Medical Association is the supreme policy-making body of that organization. It establishes its own rules of order and elects its speaker. It chooses the president and other elective officers of the Association, including 9 members of its Board of Trustees. Members of the Board are elected for a period of five years, and may not serve more than two terms. The president and president-elect of the Association are also members of the Board of Trustees by virtue of their office, with power to vote.

The House of Delegates meets twice each year. In the interval between the meetings the affairs of the Association are managed by the Board of Trustees. Reports of all actions taken by the Board are made at each meeting of the House of Delegates and are subject to approval or disapproval by the House. The Board of Trustees is also responsible for the management of the financial affairs of the Association.

The activities of the Association are carried out through a number of councils and bureaus. These cover such important programs as those of the Council on Medical Education and Hospitals, the Council on Medical Service, the Council on Rural Health, the Council on Industrial Health, the Council on Food and Nutrition, the Council on Pharmacy and Chemistry, the Bureau of Legal Medicine, the Bureau of Medical Economic Research, the Bureau of Health Information and many other activities having an important bearing on the health and welfare of the American people.

In spite of the size and complexity of the national organization an avenue is open for obtaining action or a declaration of policy on any matter originating in a local society. A resolution passed by a local organization goes to the state society and, if approved, may be presented to the national House of Delegates. Any delegate may also introduce a resolution on his own initiative, or one sponsored by a group of delegates. All resolutions are referred to reference committees of the House, appointed by the speaker. These reference committees hold hearings and report their findings and recommendations to the House. This body may approve, disapprove or amend any report of a reference committee. Any member of the Association may appear and testify before any reference committee. Other persons having a special interest

in a particular subject may be requested or permitted to testify at a hearing of these committees. It is possible, therefore, for individual local societies or state societies to have a voice in influencing the policy and in directing the affairs of the American Medical Association. The basic policy of the Association is set forth in its constitution, which declares its purpose to be "the advancement of the art and the science of medicine and the betterment of the public health." It promotes this objective through the activities of its various councils and bureaus, its scientific assembly, the *Journal of the American Medical Association* and its eight special journals. Through the Committee on Legislation and the Washington office of the Association physicians are kept informed of proposed or pending legislation in the field of health.

These bills are numerous and may be important in their relation to medicine and the medical care and welfare of the people. Whatever one's view regarding these many bills, a knowledge of their content is important, since they may affect for good or evil the future development of medicine, and the quantity, quality and availability of medical care.

Conclusions

Medicine has many facets. Its base is fundamental research in every field of science. From this grows more specific research pertaining to the particular problems of medicine. Next is the teaching of scientific medicine, making use of all the accumulated knowledge and experience of the past. But medicine is also a healing art, and the effective application of medical knowledge to the prevention and cure of disease involves a sympathetic understanding of people, of their environment, their problems as individuals, and their way of life. Medicine also involves an understanding of the social and economic factors concerned in the production, cost and distribution of medical care. It follows, then, that the continued activities of the physician must touch on many fields if he is to discharge his true mission of advancing the art and science of medicine and the betterment of the public health.

MEDICAL PROGRESS

EXFOLIATIVE CYTOLOGY

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BOSTON

THE science of exfoliative cytology has followed a pattern of development quite similar to that of other diagnostic clinical aids now widely used and generally accepted. First, one saw the reports confirming Papanicolaou's observations; these were closely followed by papers describing the results of similar studies on material from other areas of the body. Next, the pioneer workers concerned themselves with efforts to improve their accuracy, both by extending their experiences and by introducing modifications in their technic of preparing the specimens for examination. This work still goes on, but exfoliative cytology is now in the advanced stage of development where unbiased review of the accumulated experience permits one to define the indications for its use and to appraise its value.

A vast literature has accumulated in this field very rapidly, and it is no small task to organize the bibliography alone. This has been accomplished most successfully by Hoffman and Dhyse,[1] of the National Cancer Institute. They have prepared a compendium of references apparently complete and admirably arranged and cross-indexed. This booklet will be consulted with gratitude by anyone who seeks to explore the subject in any detail. A glance through it reveals that the cytologic method has been applied to every body cavity and organ with success in identifying malignant elements. It is universally agreed that cells desquamated from malignant tumors in most cases can be recognized for what they are. Detection of cancer while it is small and still entirely unsuspected should therefore be the first duty of the cytologist, but two factors are preventing more widespread use of this inexpensive method of detection. The first is the scarcity of trained and dependable cytologists and cytotechnicians; this will be remedied in time. The second is the fact that cytologic reports are subject to error and are, on occasion, falsely negative or falsely positive.

False-Negative Reports

The cytologic false-negative error occurs in cases in which cancer exists but in which the cytologist reports that no malignant cells were seen. Only two explanations are possible: either no malignant cells were on the slide or they were present and not recognized. The second is responsible for mistakes surprisingly often, and every cytologic laboratory has found that a review of its false-negative slides shows

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many cases in which malignant cells were actually present all the time. This points to the human factor in a method that depends exclusively on visual recognition for its success. Any staining technic that makes the malignant cells more obvious will reduce this error, and a variety have been reported. Some work has also been done in which other properties of the malignant cell are utilized to call attention to its presence, such as the uptake of radioactive or fluorescent dyes.[2] One may predict, however, that the most practical approach to the problem will be an improvement in the method of selecting personnel for training as cytologic technologists, since facility in visual recognition is a human characteristic easily identified and measured by appropriate testing. Surely, a laboratory staffed with properly chosen and adequately trained technicians, where all smears are independently screened by two or more persons, will keep the human error to a minimum.

Still another way to reduce the false-negative error is illustrated by technics involving mechanical scraping[3,4] or rubbing[5] of the tissue under study. This is effective by increasing the number of malignant cells on the slide; indeed, they are often present in clumps and fragments that almost justify the name of tiny biopsy specimens. Centrifugation has been used to concentrate the cells since the earliest days of cytology. Fawcett and Vallee[6] have added a valuable refinement. Using fluid layers of different densities, they have been able to separate red blood cells and other elements that may obscure and interfere with interpretation from the sediment containing the malignant cells.

False-Positive Reports

The cytologic false-positive error includes all cases in which malignant cells are reported present in the smear but no cancer can be found in the patient. This error does not lend itself to precise analysis like the false-negative reaction. Indeed, it soon carries the discusser into realms almost purely philosophic, for he must eventually answer the question, What is cancer? Many false-positive reports are truly errors of interpretation and are later recognized as such. These are most frequent with the inexperienced reader. Some, however, are on the basis of unusual cell forms provoked by nonmalignant local disease, and it is a wise cytologist who requests a modicum of clinical data on the patients he knows only through his microscope and who postpones final reporting on difficult cases until factors that may confuse the picture have been corrected. The best illustration of this is also the most common one, estrogen deficiency and its effect on the vaginal cytology.

A problem arises in cases in which the smear is positive repeatedly and unequivocally but no growth can be detected. In some cases the cells can be traced eventually to tumors of microscopic size.[7] In others the passage of time permits cancer to become apparent where none could previously be demonstrated. Still other cases never come to a satisfactory explanation, and the smear may revert to negative without treatment.[8] The situation is analogous with the behavior of some carcinomas in situ[9] that have disappeared while under observation with no treatment other than the biopsies. Obviously the false-positive smear is the clinician's nightmare, because most repeatedly positive smears eventually prove to have come from cancer. In such a circumstance he is under great pressure to excise the organ (usually the uterus and cervix) most likely to harbor the disease, although his conscience will tell him that the indication does not justify the operation and that he may be missing a tiny tumor in some other location.

Value as a Screening Procedure

One fact frequently brought forward in opposition to the indiscriminate use of the smear as a screening process is the low yield in terms of *unsuspected* cancers[10] detected. To put it in another way, the cost per case of cancer so discovered is high, the incidence of unsuspected cancer in healthy people being very low. One must leave it to the social economists to say how much money is too much to pay for each case of symptomless cancer discovered and brought to treatment. On the other hand one can point out the obvious fact that any screening test becomes more efficient in direct proportion to the likelihood of cancer in the sample of population examined. Since there are already many well controlled clinical and public-health studies to indicate what factors show a high correlation with specific tumors[11,12] the first practical step to be taken is to apply screening methods to groups of people thus preselected.

In summary it may be said that exfoliative cytology is a superior method for detecting asymptomatic cancer. The examination of cytologic material for screening purposes should be concentrated on groups of persons selected by factors known to be associated with a high incidence of specific malignant tumors, at least until qualified cytologists are everywhere available. Both the physician and the patient must understand and accept the capabilities and limitations of the method before it is offered. The occasional lesion that is missed cytologically is not adequate cause for sweeping condemnation; by the same token, the concern aroused by the unexpected suspicious or positive smear can be resolved only after the inconvenience of further careful examination and study.

Value in Diagnosis

The cytologic method is of value also in diagnosis. This refers to situations in which a lesion of some sort is known to be present and may be considered quite apart from the problem of "detection" discussed above. I would include cases in which cancer has previously been treated; for there the smear may help one

decide if therapy has been effective or if a recurrence is present.[13] The most accurate way to tell whether a tumor is malignant or not is by means of tissue biopsy. When the growth is inaccessible, however, and particularly when the patient's general condition makes exploratory operation truly dangerous, cytologic investigation of fluids from the area under suspicion may give enough additional information to permit a more accurate estimate of the risks involved.

The future will see the cytologist invited into the operating room itself for the help he can give the surgeon. One author[14] has reported a technic of making smears rapidly from lymph nodes and using the findings as a guide in deciding the extent of node excision in conjunction with surgery for cancer of the cervix. Others[15] have examined neurosurgical material with help in doubtful cases. In many areas of the body surgery can now be extended with reasonable safety to limits never previously envisaged, and, as a consequence, the question is raised more and more frequently whether treatment may not sometimes be more radical than the disease warrants. Obviously, the one fact that can decide this question is the presence or absence of microscopic extension of cancer at the periphery of dissection. Frozen-tissue examination is a help, but only if the pathologist knows where to take the section for study, and in the absence of gross tumor this is guesswork. One can visualize the possibility of making multiple smears from the areas most likely to be involved and then using the tissue technics in the specific localities that show a suspicious cytologic picture.

Use in Research

Exfoliative cytology is finding increasing use as a tool for investigation and research. With it one can observe changes in the morphology and numbers of cells desquamated from any area under study. The observations can be repeated as often as the investigator desires because no discomfort is involved and because the tissues are not distorted or injured. Such a program is being used in many clinics to gather facts about the earliest forms of cancer,[16,17] an area of knowledge much in need of elucidation. The pattern of effects produced by nonsurgical therapy can often be followed and even plotted on a graph, as Graham[18] has done in cases of cancer of the cervix during and after radiation treatment. This particular study has graduated from the research laboratory now since a more recent paper reporting the five-year follow-up status on the same patients[19] demonstrates a significant and striking correlation between cytologically good radiation response and "cure."

Clinical Cytology

Although Papanicolaou is himself an anatomist the major impetus to the development of this method during its early years came from clinicians who had access to patients and foresaw its usefulness. Few clinicians had the time to spend in learning and practicing cytologic diagnosis; their interest, therefore, stimulated the evolution of a new medical species, the full-time clinical cytologist. By its very nature, however, the technic falls most naturally within the area already under the supervision of the pathologist. Acceptance by this specialty has now become almost universal, but the process of assimilation must proceed slowly, particularly in the matter of responsibility for training and supervision. At present all three groups —clinicians, cytologists and pathologists—are active and concerned in the problems of exfoliative cytology, and it was quite natural that their common interest should result in the formation of a group known as the "Inter-Society Cytology Council" with an executive committee and an active membership.[20] The meetings of this body will serve the basic purpose of offering a forum for the exchange of ideas and early dissemination of information. In addition one hopes it will achieve its goals in the direction of formulating standards for the accreditation and supervision of personnel and laboratories, and for the proper evaluation of improvements and advances in the method.

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References

1. *A Bibliography of the Cytologic Diagnosis of Cancer.* 114 pp. Edited by E. F. Hoffman and F. J. Dhyse. Bethesda: National Cancer Institute of the National Institutes of Health, Federal Security Agency, 1952.
2. Friedman, H. P., Jr. Use of ultraviolet light and fluorescent dyes in detection of uterine cancer by vaginal smear. *Am. J. Obst. & Gynec.* **59**:852-859, 1950.
3. Panico, F. G., Papanicolaou, G. N., and Cooper, W. A. Abrasive balloon for exfoliation of gastric cancer cells. *J.A.M.A.* **143**:1308-1311, 1950.
4. Ayre, J. E. Vaginal and cervical cytology in uterine cancer diagnosis. *Am. J. Obst. & Gynec.* **51**:743-750, 1946.
5. Gladstone, S. A. Diagnosis of early carcinoma of cervix by sponge biopsy. *New Eng. J. Med.* **241**:48-52, 1949.
6. Fawcett, D. W., and Vallee, B. L. Some new approaches to cytologic diagnosis of cancer from serous fluids. *Bull. New Eng. M. Center* **12**:224-228, 1950.
7. Graham, R. M., and McGraw, J. Investigation of "false positive" vaginal smears. *Surg., Gynec. & Obst.* **90**:221-230, 1950.
8. Younge, P. A. Carcinoma in situ of cervix. In *Monographs on Surgery.* 508 pp. Edited by B. N. Carter. New York: Nelson, 1951. Pp. 20-35.
9. Scapier, J., Day, E., and Durfee, G. R. Intraepithelial carcinoma of cervix: cytohistological and clinical study. *Cancer* **5**:315-323, 1952.
10. Getting, V. A., and Lombard, H. L. Evaluation of pilot clinics: mass screening or health-protection program. *New Eng. J. Med.* **247**:460-465, 1952.
11. Lombard, H. L., and Potter, E. A. Environmental factors in etiology of cancer. *Acta de l'Union internationale contre le Cancer* **6**: 1325-1333, 1950.
12. Barrett, M. K. Avenues of approach to gastric-cancer problem. *J. Nat. Cancer Inst.* **7**:127-157, 1946.
13. Meigs, J. V., Graham, R. M., Fremont-Smith, M., Kapnick, I., and Rawson, R. W. Value of vaginal smear in diagnosis of uterine cancer. *Surg., Gynec. & Obst.* **77**:449-461, 1943.
14. Dearing, R. Diagnosis of malignant involvement of lymph nodes by smear technique. *J. Obst. & Gynaec. Brit. Emp.* **59**:385-387, 1952.
15. Larson, C. P., and Reberger, C. C. Smear method for rapid diagnosis of neurosurgical material. *Am. J. Clin. Path.* **22**:916, 1952.
16. Gates, O., MacMillan, J. C., and Middleton, M. Vaginal smear as means of investigating early carcinoma of cervix. *Cancer* **2**: 838-844, 1949.
17. Pund, E. R., and Blumberg, J. M. Cancer in situ (preinvasive) of cervix uteri. In *Monographs on Surgery.* 508 pp. Edited by B. N. Carter. New York: Nelson, 1951. Pp. 42-63.
18. Graham, R. M. Effect of radiation on vaginal cells in cervical carcinoma. I. Description of cellular changes. *Surg., Gynec. & Obst.* **84**:153-165, 1947.
19. *Idem.* Prognosis of cancer of cervix by vaginal smear: correlation with five year results. *Surg., Gynec. & Obst.* **93**:767-774, 1951.
20. Fletcher, P. F. Inter-Society Cytology Council. *Cancer* **6**:192-194, 1953.

MEDICAL INTELLIGENCE

WORK PRESCRIPTION

A Co-operative Procedure with the Practicing Physician in Vocational Rehabilitation

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BOSTON

THE phrase "light work," used so often by physicians to a patient or to his family or included in reports to insurance companies or welfare agencies, has little meaning by itself.

All work requires nearly maximal effort and in employment to-day every worker, whether bookkeeper or longshoreman, is expected to deliver a full day's work to the limit of his abilities. To the partially paralyzed or the cardiac patient, even getting to and from work may be arduous although the work itself may be "light." To the psychoneurotic or the anxiety-ridden person intense concentration may be more difficult than a day's labor in the streets for a healthy man. All work, then, is "light" or "heavy," depending on the physical and emotional capacity of the individual worker. It is self-evident that what may be "light" for one person may be strenuous for another.

One should consider, then, how a recommendation for "light work" may affect the patient to whom it is addressed. Though puzzled, he attempts to follow this poorly defined medical prescription, perhaps with the consequence that he finds no work and begins to question his personal adequacy. Because of repeated failures to obtain "light work" he becomes confused and discouraged and does not put his best foot forward in his interviews with prospective employers. Family quarrels have occasionally developed from a misunderstanding of such recommendations. Wives have charged their husbands with indolence because they could not obtain employment. In some cases the medical recommendation of "light work" has deprived patients of their eligibility for assistance under the provisions of the Aid to Dependent Children and Disability Assistance programs, and has jeopardized the rights of workers under the Workmen's Compensation Act.§

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§The opinions stated in this article are those of the authors and are not intended as a policy statement of the Massachusetts Division of Vocational Rehabilitation.

When he prescribes "light work" for a patient, a physician may be aware, through years of experience and as a result of thorough knowledge of the patient's limitations, of the effort that such a patient is able to make. But how clear is the job picture in the doctor's mind? In general, physicians have not evaluated the patient's capabilities or limitations and compared them to the demands of specific jobs. They cannot know the various types of activity that each job entails. Even after careful perusal of the *Dictionary of Occupational Titles,* one can never be sure what activities will be required in a given position. For example, the job of shipping clerk in one company may be purely clerical, whereas, in another company, it may be so strenuous as to be suitable only for a vigorous and athletic worker.

The physician may avoid many disappointments for his patients by turning to the resources of the Commonwealth available for people of working age whose physical or emotional disabilities are substantial employment handicaps and yet who may be expected, if properly served, to become employable within a reasonable length of time. Co-operative procedures with the participation of physician, medical social workers in hospitals and clinics, and vocational counselors in the State Division of Vocational Rehabilitation should lead to a job objective that meets the physical capacities as well as the over-all interests and abilities of the patient. Of the team the patient himself is the most important member; the family must also understand its part in the co-operative procedure. It should be emphasized that work capacity depends not only on what a person can do but on what he believes he can do. A successful program works not *on* a patient but *with* him.

To fulfill his part in the plan, the physician should concentrate his attention on specific activities that the patient may or may not be able to do. Preferably, the focus should be on the positive side. To achieve some degree of uniformity, a sample chart of activities has been suggested (Table 1). In completing this chart, the doctor indicates the guideposts needed by his patient in daily routine activities and also provides a prescription for the vocational counselor whose responsibility is to help the patient obtain employment. The type of work that meets the patient's needs is determined only in part by his physical capacity. By describing permissive activities for the patient in accordance with the chart, the physician provides the basis for the complete evaluation necessary in planning for the vocational objective. The whole team must decide upon the patient's total personality in both genetic and dynamic terms and must also assess his readiness for vocational rehabilitation.

The final determination of employability, distinct from physical ability to work, must be the judgment of the vocational counselor. He is the member of the team who knows the industrial opportunities open within a given community, as well as the hiring speci-

fications of employers at a given time, and who can fit together the various contributions of the other members of the team into a workable plan. In practical terms, the likelihood of getting work depends less on the physical capacity of the patient than on such

TABLE 1. *Activities Chart.*

ACTIVITY	NO LIMITATION	SOME LIMITATION	IN HOURS
Walking			
Climbing (stairs)			
Lifting (in pounds)			
Carrying (in pounds)			
Stooping			
Running			
Pushing			
Pulling			
Reaching			
Environmental conditions to be avoided (specify):			
Total hours of activity recommended at this time:			
in six months:			
Use of public transportation recommended Yes No			
Other limitations—specify:			
Other comments (describe patient's major capabilities):			

factors as age, education, and recency of work experience. Moreover, the patient's personality, his ability to get along with others and his drive for independence are added elements in his employability. In the last analysis, finding opportunities for employment depends to a large extent on the knowledge of the labor market at a given time and on an acquaintance with the hiring specifications of employers within that labor market.

CASE REPORTS

CASE 1. A 59-year-old man with a diagnosis of rheumatic heart disease with mitral stenosis and insufficiency and atrial fibrillation, complicated by osteoarthritis of the lumbar spine, was referred to the Massachusetts Division of Vocational Rehabilitation by the Massachusetts Heart Association for help with placement in employment suitable to his disabilities. On digitalis he was well compensated. Although born in Russia, he read and wrote English well. He had been out of employment for 13 months, living on his savings and income from his wife's part-time employment. His work history had been excellent, mainly as a shipper in department stores. He knew how to pack china and fine clothing and was familiar with the mailing zones, both domestic and foreign. The problem was to return him to employment suitable to his disability, utilizing his past experience. By a chain of fortuitous circumstances, a shipping job was found in a small company. The job was studied and found to be within his physical capacities, and the company was willing to make some minor job adjustments. He was placed in an area of familiarity, the emotional trauma associated with job change (especially for an older worker) thus being minimized. In this case successful job placement depended on searching for a *specific* job rather than "light work" in general.

CASE 2. A 28-year-old single man was admitted to a tuberculosis sanatorium in 1939 with a diagnosis of bilateral pulmonary tuberculosis. His work experience was in unskilled jobs, such as porter and watchman, probably owing to the fact that he entered the labor market during the depression, having graduated from high school in 1930. He was the only child and the sole support of a widowed mother. He was hospitalized from 1939 to 1951, when he was discharged from the sanatorium, the tuberculosis apparently having been arrested. His mother had been forced to apply to public welfare for support during his hospitalization. He was referred to the Massachusetts Division of Vocational Rehabilitation by the physician who was following his case after discharge. The problem was to provide a skill within his physical and intellectual capacities and also within his interests. It was decided by the patient and the vocational counselor that television repair would be a suitable vocational objective. The doctor agreed with this plan in conference with the vocational counselor. After training of about a year and a half, the patient was placed as an electronic technician, however, this job being much less strenuous than that of a television repairman and still in line with his training. Thus, despite his present age (43 years) and long hospitalization, the client is suitably employed, vocational training having provided not only a skill but also an opportunity for much needed resocialization before he entered the employment world.

SUMMARY AND CONCLUSIONS

The physician is expected to focus on the permissive activities that a patient may undertake by completing an estimate of physical activities rather than simply recommending "light work."

Referral of the handicapped person to community resources, such as the State Division of Vocational Rehabilitation, which are specially structured for vocational counseling, training and placement, is urged.

Selective placement for employment depends not only on a handicapped person's physical and mental capacity but also on age, education, quality and recency of work experience, personality structure and the particular opportunities within a given labor market at a given time.

BY THE LONDON POST

Medical Aspects of Road Safety — The Doctor and His Pen

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LONDON, ENGLAND

IT was recently predicted that in ten years road casualties in Britain will have risen to an annual total of 350,000, an increase of 40 per cent over the present figure. Two committees of the British Medical Association have studied some of the medical factors involved. One of these committees considered the question of alcohol. In its report, entitled "The Recognition of Intoxication," the Committee states its belief that people under the influence of alcohol are responsible for many more accidents than official records indicate. They think that the police are reluctant to assign alcohol as the cause of an accident unless the evidence is strong, and they believe that

many doctors called on to give evidence are not sufficiently experienced in the medical problems of alcoholic intoxication. The report describes the procedure that a doctor should adopt when examining a suspect and discusses the value of estimating the alcohol content of body fluids. Such analysis is not often obtained in this country, and no particular blood or urine level is accepted by law as signifying that the suspect was culpably drunk. On the other hand a negative finding can exonerate the person under suspicion, and when he is examining a person for drunkenness, it is clearly the doctor's first duty to exclude any pathologic condition that may simulate or exaggerate alcoholic intoxication. The formation of the British Medical Association Committee followed a request from the Minister of Transport for guidance on the suitability of diabetic patients as drivers of public-transport vehicles. Because it was considered opportune to examine the whole question of medical standards for drivers the committee carefully examined the chief medical conditions that may contribute to road accidents. In particular it stressed the importance of good visual acuity and suggested that all public-transport drivers have a test of vision every five years. No person suffering from epilepsy should be permitted to drive any form of vehicle, and the cases of hypertensive persons and those who have suffered definite cardiac infarction should be kept under individual review. Concerning diabetes, the committee admitted that wide variations of opinion exist. Some would debar all diabetic patients taking insulin from driving because of the danger of hypoglycemia, but others would permit the co-operative patient to drive. The committee recommended that a patient receiving insulin should not be engaged for the first time as a public-service driver but considered that when diabetes develops in an already experienced driver each case should be treated on its merits.

In conclusion the committee urged an intensification of research into the personal factors responsible for road accidents. Speaking on the results to date, the director of road research of the Department of Scientific and Industrial Research stated that the missing factor in determining accident proneness seemed to be associated with what the psychologists call temperament. He said that temperament changes with age and that the driver who is between forty and fifty years old has fewer accidents than one who is twenty to thirty years old. It is surprising that assets such as short reaction time and high intelligence seem less important in accident prevention than an inborn law-abiding nature, for it has been shown both in this country and in America that the bad citizen is also likely to be a bad driver.

* * *

The old tale that the doctor did not wish his patients to be able to read what he was prescribing is wearing rather thin as an excuse for habitual bad handwriting. In a letter to the *British Medical Journal* a correspondent expressed surprise that illegible writing should be considered in any way a desirable asset, and yet bad writing is no recent phenomenon among doctors. Joining in the correspondence, Mr. Geoffrey Keynes recalls that the handwriting of such notable physicians as Sir Thomas Browne and Dr. William Harvey was lamentable. Harvey's writing was so poor that his friend, Sir George Ent, made apologies for it to the president of the College of Physicians in his dedication, which was prefixed to Harvey's *De Generatione Animalium*. Mr. Keynes wonders whether some generous patron might institute prizes in the medical schools for good handwriting but then reflects that it is the graduate doctors who are the worst offenders. Of course, it may be argued that familiarity breeds contempt, for every physician carries a pen, — even if he never uses a stethoscope, — and apart from the routine of writing notes and prescriptions, the modern young physician is encouraged to resort to the metaphorical pen at every opportunity. "Publish, publish, publish man" is the advice often given to the young clinician today. It is said that in the face of present competition this method of ethical advertising is essential, and yet the wisdom of the advice may be questioned when the volume (and even the standard) of current medical literature is surveyed. Then, too, there is the doctor who forsakes entirely his stethoscope for his pen and, drawing on the experience of his practice for material, takes to writing fact or fiction. As an example of this type there was Dr. Francis Brett Young, who died this year. Coming from a medical family, he graduated from Birmingham and settled in general practice in 1907. After serving with the Medical Corps in World War I he turned to writing. He rapidly gained recognition as a novelist and continually drew upon his years of work as a general practitioner for the substance of his fiction.

Many physicians have indulged in autobiography, whereas others have written biographies. Dr. Leonard Colebrook has made a great contribution in this field by writing the life of Almroth Wright. In the book he reveals the energy that this man put into scientific research. While a young man, he won renown by his discoveries regarding immunization against typhoid, and at the age of seventy-four he was still working in his laboratory. With his own pen Wright was provocative and self-assured and apparently confessed that he made it a principle "never to write anything that won't give offence to somebody."

More lighthearted and less intense is the writing of a young anesthetist, whose two books, *Doctor in the House* and *Doctor at Sea*, are enjoying remarkable success. The former contained so many potentialities that it has been adapted for the screen. In rapid sequence three students have fun with skeletons and fun in operating rooms, with nurses, with beer, with Rugby football and with rival hospitals. Immature though this may sound it reflects a true (if exaggerated) phase of a medical student's life, and on the screen it earns an uninhibited laugh.

And, finally, there is the doctor who, having forsaken his stethoscope for his pen, in turn forsakes this for the editor's blue pencil. The influence that may be exercised from the editorial chair is great, and this has been clearly shown in the many fine tributes paid to Dr. Gerald Horner, who was editor of the *British Medical Journal* from 1928–1946 and who died earlier this year. He spoke of medical journalism as the smallest of the specialties. From his own position at the head of the specialty in this country he continually showed his interest in medicine and his intense loyalty to it. He added strength to his position by showing that he was little concerned with the politics of the day.

A word might be added in appreciation of a book, *All Creatures Here Below,* that has just come from the pen of the editor of the *New England Journal of Medicine.* "Workmanlike" was the term that Horner liked to use, since this apparently stood for him, as it did for his great predecessor at the *British Medical Journal,* Sir Dawson Williams, the sovereign quality. It seems a reasonable aim for every doctor to make his writing—whether in fact or in metaphor—workmanlike, for this surely reflects a disciplined, painstaking and accurate attitude that, in the field of medicine, it is one's clear duty to adopt.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40211

PRESENTATION OF CASE

First admission. A sixty-two-year-old salesman entered the hospital because of epistaxes and nasal obstruction.

He had been well all his life until the onset of recurring painless epistaxes from the left side of the nose six months before admission. These occurred about once a month and were accompanied by a gradually increasing sensation of nasal obstruction.

Physical examination disclosed a tumor, 2.5 by 4 by 5 cm., occupying the posterior inferior portion of the left nasal cavity and bulging from the antronasal wall. There were no other significant physical findings.

Roentgenograms of the sinuses showed a soft-tissue mass in the left posterior nasal cavity, with erosion of the antronasal wall and destruction of the maxilla. A roentgenogram of the chest was normal.

The tumor was removed, and a diagnosis of plasmacytoma was made. Postoperatively, x-ray therapy consisting of 4000 r was administered.

Second admission (three years later). After discharge from the hospital the patient enjoyed good health; he was examined twice yearly, and no evidence of recurrent nasal tumor was detected. One year before entry he had an attack of "flu" lasting three days, with malaise, fever, sore throat and hoarseness. Since then he had had several such episodes and noted that he was hoarse most of the time. A nonproductive cough became increasingly severe. Four months before entry he began to have transient shooting pains from the left side of the neck radiating across to the right side of the chest. Pain on motion was noted in the region of the right shoulder, and he had difficulty walking because of pain in the mid-lower lumbar region. A physician made a diagnosis of arthritis and gave twelve injections of a gold-containing preparation. No roentgenograms were taken. After two months of treatment the pains disappeared, and the patient again felt well except for hoarseness.

Three weeks before entry, during the course of a routine semiannual examination by his otorhinologist, a mass was discovered in the right side of the neck. Shortly thereafter another mass near the middle portion of the left clavicle appeared and grew. Although these masses were asymptomatic at first, by the time of hospital admission the patient felt as though "both collar bones were enlarged and pressing on my throat."

Physical examination revealed a well nourished man who was hoarse. The thyroid gland was palpable and was believed to be enlarged to twice the normal size. A discrete, egg-shaped mass was present in the right anterior cervical triangle. A separate, 3-cm., hard mass was present over the proximal end of the right clavicle, and another 2.5-cm. mass appeared to be in continuity with the distal third of the left clavicle. The tumors were rubbery and firm and fixed to the underlying structures; the overlying skin was freely movable. Examination of the chest disclosed no bone tenderness; the heart and lungs were not remarkable. The prostate was smooth and enlarged to twice the normal size.

The temperature, pulse and respirations were normal. The blood pressure was 150 systolic, 90 diastolic.

The urine had a specific gravity of 1.018; tests for urinary albumin, sugar and Bence-Jones protein were

negative. Examination of the blood showed a hemoglobin of 15.5 gm. and a white-cell count of 7000, with 61 per cent neutrophils, 20 per cent lymphocytes, 4 per cent monocytes, 3 per cent eosinophils and 2 per cent basophils. The red cells demonstrated slight rouleau formation. The albumin was 3.8 gm., the globulin 3.6 gm., and the alkaline phosphatase 2.3 units per 100 cc. A tracer study with radioactive iodine indicated 10 per cent uptake in forty-eight hours. Roentgenograms of the skull disclosed several rounded, punched-out areas of decreased density in the cranial vault, measuring up to 2.5 cm. (Fig. 1). There was almost complete destruction of the distal third of the left clavicle and early osteolytic changes of the distal portion of the right clavicle. The vertebral bodies were osteoporotic, and irregular areas of decreased density in the scapulas were noted. The ribs were intact.

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. William D. Sohier, Jr.*: It is too bad that on physical examination a nodule was not found beneath one of the nipples; then I should have had to discuss the four tumors that most commonly metastasize to bone. I shall start out by saying that I believe the patient had a malignant lesion and that the problem is to decide whether the neoplasm was recurrent plasma-cell tumor or a metastasis from the prostate or the thyroid gland. May we see the x-ray films?

Dr. Joseph Hanelin: The films that I have are of the last examination only. Particularly striking are the round areas of destruction in the skull (Fig. 1). There is extensive destruction of the distal end of the left clavicle and involvement of the medial end of the right clavicle. Several ribs, I believe, have appreciable lesions also. No obvious nodules are seen in the lungs. There is an erasure of some of the pedicles in the thoracic spine, indicating vertebral involvement.

Dr. Edgar B. Taft: Is the maxilla normal?

Dr. Hanelin: There is a large mass in the nasopharynx that may be arising from the maxilla.

Dr. Sohier: Is there any osteoblastic reaction?

Dr. Hanelin: No; the lesions are purely lytic.

Dr. Sohier: And the cranial vault is not thickened.

Dr. Hanelin: No; there is no thickening of the vault.

Dr. Sohier: Let me first discuss the prostate, which was smooth and enlarged to twice the normal size. I do not believe that this was cancer of the prostate with metastases to the bone because such lesions are almost always osteoblastic and there was only osteolysis in this case. Also, the alkaline phosphatase was within normal limits. Commonly men of this age, sixty-two, have enlarged prostates. Although there may have been small foci of adenocarcinoma on histologic examination, I certainly am unable to make that diagnosis; therefore, I believe this patient had merely benign prostatic hypertrophy.

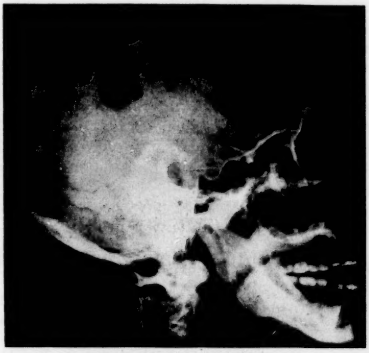

Figure 1. *Lateral Roentgenogram of the Skull, Showing Multiple Lytic Areas.*

The thyroid gland was palpable and believed to be enlarged to twice the normal size. Were its shape and consistence noted in the record?

Dr. Marshall K. Bartlett: About a week before admission I saw this man with the otorhinologist who had been following him. At that time the thyroid gland could be felt. There was one mass in the upper right pole and what I interpreted as a chain of enlarged lymph nodes along the jugular vein on the right side; they were firm, smooth and nontender. The soft-tissue mass over the outer left clavicle, which was very apparent when he was in the hospital, was not detected at that time.

Dr. Sohier: Of course, I wondered whether this was a cancer involving the thyroid gland with metastases to the bone. Mention is made of a tracer study with radioactive iodine that showed a 10 per cent uptake in forty-eight hours; that is low. It could mean either that the thyroid gland was not interested in iodine or that other tissue was equally avid in taking up the iodine. Were counts taken over the tumor masses or, equally important, was the urine collected to ascertain how much of the total radioactive iodine was excreted at the end of that period?

Dr. Farahe Maloof: The urine was not collected; the extrathyroidal tissue in the neck was not specifically checked for radioactivity.

Dr. Sohier: I am not sure that I know what the significance of the low uptake of radioactive iodine is. Perhaps the patient had invasion of the thyroid gland with tumor tissue or some sort of chronic thyroiditis with enlargement of the gland and low uptake of radioactive iodine. These bony metastases do not look

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like the metastases from the thyroid gland; they are small, discrete and numerous. A good part of the spine was osteoporotic. Although it is possible that the patient had carcinoma of the thyroid gland with metastases to bone, I consider it is unlikely.

It seems more likely that he had a recurrent plasma-cell tumor. Stout and Kenney,[1] in 1949, reviewed 100 cases of plasma-cell tumors that arose in the nasopharynx and found it difficult to make any statement about recurrence. Of those 100 cases about 50 were available for follow-up study; approximately 12 cases within three years showed typical multiple myeloma. In the case under discussion there was not only the history of removal of a plasmacytoma, but there is the new information that Dr. Hanelin gave me regarding local recurrence at the end of three years and multiple discrete osteolytic bony metastases without evidence of pulmonary metastases. It is interesting that in the 100 cases that Stout and Kenney reviewed there was no pulmonary metastasis. For that reason some groups believe that these lesions do not represent true metastases but are actually multicentric origins of the tumor, since it would be difficult for blood-borne emboli to be carried through the lungs to bone and yet so rarely to deposit metastases in the pulmonary tissue. Geschickter and Copeland[2] report that metastases of plasma-cell tumors to the thyroid gland are the commonest soft-tissue metastases outside the hemopoietic tissue — by hemopoietic they mean not only bone marrow but also liver, spleen, lymph nodes and tonsillar tissue — so that the total number of myelomas metastatic to the thyroid gland is small. However, I believe that in the case under discussion there was plasma-cell infiltration into the thyroid gland. Therefore, my diagnoses are recurrent multiple myeloma, with involvement of bone, lymph nodes and thyroid gland, and benign prostatic hypertrophy.

A PHYSICIAN: Was the elevated serum globulin a differential point?

DR. SOHIER: I meant to mention that. Yes; I think it is in favor of multiple myeloma. I might also mention that the lack of anemia and of Bence-Jones protein does not discourage me. The incidence of Bence-Jones protein in proved multiple myeloma varies from 60 to 90 per cent according to how diligently one looks for it. It may be that if this was multiple myeloma Bence-Jones protein will be found in the urine later on in the course of the disease.

A PHYSICIAN: Are not the skeletal lesions pathognomonic of multiple myeloma?

DR. HANELIN: These lytic lesions are fairly characteristic of myeloma, but may also occur with disseminated lymphoma or carcinoma.

CLINICAL DIAGNOSIS

Carcinoma of thyroid gland.
?Multiple myeloma.

DR. WILLIAM D. SOHIER, JR.'S, DIAGNOSIS

Multiple myeloma involving bone, lymph nodes and thyroid gland.

ANATOMICAL DIAGNOSIS

Multiple myeloma involving bones and thyroid gland.

PATHOLOGICAL DISCUSSION

DR. TAFT: This patient had a typical plasma-cell myeloma. A needle biopsy of what was said to be a shoulder mass, presumably the clavicle, and later a biopsy of the thyroid gland both showed well differentiated plasma-cell myeloma. The biopsy of what was thought to be the thyroid gland showed no thyroid tissue so that we could not be sure of its exact origin.

It seemed to us that this case fits in with the first group of the 21 cases of plasma-cell myeloma of the upper respiratory passages and mouth described by Ewing and Foote,[3] of the Memorial Hospital in New York City. In this first group of 9 patients the presenting plasma-cell tumor was merely a manifestation of generalized disease. As in this patient the clinical diagnosis at first was of a malignant tumor until the tumor was biopsied. The physicians who saw this patient on his first admission thought that he had a squamous-cell carcinoma until they received the biopsy report. As far as we can tell from the record he actually was not thoroughly studied at that time. No x-ray films were taken except those of the skull and chest initially so that there was no real search for other sites of myeloma. Ewing and Foote said, "Surely the fact that one-third of the patients who presented on the Head and Neck Service of this hospital (from 1936 to 1950) with plasma-cell tumors were really suffering from the multiple form of this disease clearly underlines the necessity for more complete investigation every time this histological picture is reported by the pathologist." If this patient had been investigated more thoroughly after the diagnosis had been made his generalized disease might have been recognized somewhat earlier. From the practical point of view I doubt if this would have done him much good; he has survived for three years so far and may well survive considerably longer.

DR. EARLE M. CHAPMAN: The possibility that the goiter was benign interested me. The tumors that were present in the neck, I thought, could be related to the nasal tumor that had been found to be radiosensitive. The patient also had arthritis and had been taking large amounts of para-amino-salicylic acid for quite a long time. From the thyroid point of view this is very interesting; it has been found that para-amino-salicylic acid depresses the uptake of radioactive iodine and may stimulate thyroid growth. It is uncertain when he stopped the drug — perhaps a week or so before admission. With this thought we were particularly interested in knowing whether the thyroid gland was the kind that we see after ingestion

of a goitrogen or whether this was a primary or secondary tumor. Dr. Bartlett, when you did the biopsy, did you think there was an adequate piece of thyroid gland?

DR. BARTLETT: To clarify the matter of the biopsies, the first one was taken with a needle from the soft-tissue lesion over the outer end of the clavicle. The biopsies of the thyroid gland and the adjacent lymph node were done under direct vision; I am sure that one or more of the pieces that we removed were actually from the thyroid gland.

DR. TAFT: The pieces we received showed only plasma-cell myeloma and had no distinguishing anatomical features. The replacement of the thyroid tissue by tumor probably accounts for the low uptake of radioactive iodine.

REFERENCES

1. Stout, A. P., and Kenney, F. R. Primary plasma-cell tumors of upper air passages and oral cavity. *Cancer* **2**:261-278, 1949.
2. Geschickter, C. F., and Copeland, M. M. *Tumors of Bone.* Third edition. 810 pp. Philadelphia: Lippincott, 1949.
3. Ewing, M. R., and Foote, F. W., Jr. Plasma-cell tumors of mouth and upper air passages. *Cancer* **5**:499-513, 1952.

CASE 40212

PRESENTATION OF CASE

A forty-eight-year-old woman was admitted to the hospital because of occipital headaches, vomiting and weakness.

Twelve years previously the patient began to have severe episodes of "smothering," with marked dyspnea and orthopnea but without chest pain or ankle edema. After one of these attacks she was kept in bed for six weeks and started on digitalis, which she continued to take periodically and sporadically. Thereafter, she was fairly well except for episodic attacks of dyspnea, orthopnea and paroxysmal nocturnal dyspnea, which disappeared when she again took digitalis. Three years before entry, when symptoms of polydipsia, polyuria and polyphagia developed, examination revealed diabetes and a high blood pressure. She refused to take insulin and was placed on a diabetic diet and given digitalis; her physician stated that the urine was "loaded with sugar" on all subsequent examinations. Since then her general health had allegedly been quite good except for the periodic episodes mentioned above. Six months before admission she began to have persistent dyspnea, orthopnea and paroxysmal nocturnal dyspnea; ankle edema and episodes of painless jaundice developed. There was no chest pain, hemoptysis or pain or tenderness in the legs. In spite of treatment with digitalis, diuretics and salt restriction all the symptoms became progressively worse. Eight days before admission occipital headaches, epistaxis, drowsiness, increasing weakness, vomiting and a nonproductive cough developed. Five days later she noticed blurring of vision in the right eye. All these symptoms became progressively worse in spite of treatment.

Her appetite had remained good, but within a few hours after each meal she vomited all that she had eaten. There had been no diarrhea, melena, hematemesis, skin rashes or purpuric spots. She had had frequency, urgency and nocturia (two or three times) for many years. She had steadily lost weight in the few months before entry. She had had typhoid fever at sixteen and scarlet fever at thirty years of age, without known sequelae. She had a severe prolapse of the pelvic organs after the birth of a child twenty-five years previously; this had never been repaired.

Physical examination revealed a well nourished woman who was moderately dehydrated and appeared chronically ill. Funduscopic examination showed punctate and longitudinal hemorrhages along the course of the vessels, moderate arteriovenous nicking and tortuosity, some exudates and blurring of the disk margins. The neck veins were very slightly distended and did not pulsate. There were dullness and absent breath and voice sounds at the base of the right lung, with occasional scattered rales above the line of dullness and at the left base. The heart was enlarged, the border of dullness extending to the anterior axillary line; there was a Grade 2 apical systolic murmur and a diastolic gallop that was heard in the right third interspace. The aortic second sound was louder than the pulmonic. There was a diastasis of the rectus muscle and a soft, cystic, rounded mass in the right upper quadrant. The abdomen was pendulous. A slightly tender liver was palpable 2 fingerbreadths below the right costal margin, and the tip of the spleen was barely palpable on deep inspiration. There was a marked procidentia, with edema and erosion of the cervix. There was + + + + pitting edema of the feet and legs, extending up to the thighs, and + + sacral edema. The hands were puffy.

The temperature was 99°F., the pulse 82, and the respirations 20. The blood pressure was 210 systolic, 100 diastolic.

The urine had a specific gravity of 1.015 and gave a + + + + reaction for albumin, a + reaction for acetone and an olive-green sugar reaction; the sediment contained 10 to 15 white cells, 2 to 5 red cells and 2 to 5 granular and hyaline casts per high-power field. Examination of the blood demonstrated a hemoglobin of 6 gm. per 100 cc. and a white-cell count of 10,400, with 85 per cent neutrophils. The nonprotein nitrogen was 119 mg., the blood sugar 179 mg., the serum bilirubin less than 0.5 mg. direct, the cholesterol 188 mg., the total protein 6.37 gm. (with an albumin-globulin ratio of 1.8), the calcium 8.8 mg., and the phosphorus 8.6 mg. per 100 cc.; the serum sodium was 140 milliequiv., the chloride 101 milliequiv., the potassium 5.6 milliequiv., and the carbon dioxide 16.3 milliequiv. per liter. The pH of the blood was 7.20. Roentgenograms of the chest showed the heart to be considerably enlarged, predominantly in the region of the left ventricle. There was a moderate amount of fluid in the right pleural space. The hilar and pulmonary shadows were en-

gorged, and there was a hazy density throughout both lung fields. In the region of the anterior and medial basal segments of the right lower lobes there was a hazy, homogeneous density lying against the major fissure. X-ray films of the abdomen suggested some increase in abdominal fluid; in the lateral view a localized protuberance, 10 cm. in diameter, extended from the anterior lower abdominal wall and had the same texture and density as the adjoining subcutaneous fat. An electrocardiogram revealed left-axis deviation and nonspecific ST-segment and T-wave changes.

The patient was treated with a diabetic diet, intravenous therapy, transfusions of packed red cells, digitalis, Mercuhydrin and sedation. A stomach tube was inserted. On the second hospital day the urine was free of sugar and the blood sugar was 118 mg. per 100 cc. The reaction for acetone in the urine varied between negative and + + +. She continued to vomit, became progressively weaker and dehydrated, complained of pains in the calves, finally became confused and then comatose, began to have twitchings and purpuric spots and died on the thirty-first day; the nonprotein nitrogen and carbon dioxide remained unchanged during the hospital course.

Differential Diagnosis

Dr. Alexander Leaf*: The history is that of a forty-eight-year-old woman who for twelve years had intermittent symptoms of left-sided heart failure. Nine years after the onset of the cardiac complaints, symptoms of diabetes developed, and an elevated blood pressure was found. More recently, symptoms of hypertension, congestive heart failure, renal insufficiency and poorly controlled diabetes combined to cause her final hospital admission.

May we see the x-ray films?

Dr. Joseph Hanelin: Roentgenograms of the chest show moderate, generalized cardiac enlargement and engorgement of pulmonary vessels bilaterally. A small amount of fluid is present in each pleural cavity, more on the right. A homogeneous zone of density is observed within the anterior basal portion of the right lower lobe that could represent localized edema or pneumonic consolidation, possibly on the basis of infarction. In the abdomen there is a large amount of intra-abdominal fat and any ascites, at most, is minimal. The right lobe of the liver is prominent. Renal outlines are faintly traced. The kidneys are of about equal size and tend to be small. In the lateral projection of the abdomen a rounded density is observed extending anteriorly from the lower abdominal wall. Most likely this is a ventral hernia.

Dr. Leaf: Dr. Hanelin, do you see any evidence of an adrenal mass?

Dr. Hanelin: No; there is nothing abnormal that I can visualize in the region of the adrenal glands.

*Assistant physician, Massachusetts General Hospital.

Dr. Leaf: There is little in the case presentation to permit me to make a specific diagnosis. The history seems to stress the episodic nature of onset of this woman's illness. The symptoms of "smothering" dyspnea and orthopnea suggest acute pulmonary congestion. In a thirty-six-year-old woman without preceding known heart disease these symptoms might have been the result of a cardiac arrhythmia—paroxysmal atrial tachycardia or flutter; however, the patient should have had some awareness of the rapid heart action. Such a cardiac diagnosis would not explain the subsequent severe hypertension, which was first recorded in the protocol as having been present three years before admission.

Much of this patient's course could be explained on the basis of severe hypertension alone. The early symptoms of left-sided heart failure and the subsequent generalized edema, visual disturbances and terminal uremia all fit this diagnosis. The occurrence of hypertension severe enough to produce episodes of left-sided heart failure at the age of thirty-six is unlikely to be associated with a twelve-year survival. It is also disturbing that hypertension was first mentioned after nine years of illness. That diagnosis is ordinarily readily made. Information regarding the presence or absence of a family history of hypertension would have been helpful in diagnosis.

Diabetes mellitus likewise could account for a large portion of the patient's difficulties. With its attendant vascular complications it could cause hypertension, congestive heart failure, retinal changes and renal failure. The marked albuminuria and peripheral edema, together with hypertension, renal failure and retinopathy, suggest the Kimmelstiel–Wilson syndrome. However, the normal serum total protein concentration and albumin-globulin ratio exclude the nephrotic syndrome as the cause of the edema. More important is the fact that the history clearly states that symptoms of pulmonary congestion, which I think must have had a cardiac basis, were present nine years before the symptoms of diabetes — polydipsia, polyuria and polyphagia — developed. Thus, it is diffcult to attribute the preceding cardiac symptoms to the diabetes.

One would perhaps be more comfortable in making a single diagnosis, which might explain the hypertension, diabetes, congestive heart failure and renal failure in the sequence in which they occurred. The history was written in a manner that tempts one to make such a diagnosis. Again, I refer to the emphasis on the episodic nature of the symptoms, which was stressed even six months before admission. It is unfortunate that more details of one of these "smothering" episodes are not available in the history. The pulse rate and rhythm, the color of the skin and mucous membranes, the presence or absence of palpitation, headaches, visual disturbances, chest pain, dizziness, perspiration and tremor, the examination of the chest and heart, the duration of the attacks and,

above all, the blood pressure would be most interesting information for us to know now.

In spite of the lack of detail the very fact that the patient's illness had an episodic early course requires that one mention the possibility of pheochromocytoma. This tumor would account for the early attack of "smothering," the development of diabetes mellitus and finally the persistent severe hypertension with terminal cardiac and renal failure. Nothing I can think of would include the alleged episodes of painless jaundice, and in the absence of objective evidence of jaundice during admission I must disregard what is usually important evidence in any history. The age at onset of the disease is compatible with pheochromocytoma. About half the patients with this condition have persistent hypertension by the time the diagnosis is made, and the course may then mimic malignant hypertension, as in this case. Adrenocortical tumors may be associated with hypertension and diabetes but would not cause intermittent symptoms such as this patient allegedly had.

The terminal event seems to have been due to a combination of uremia with its acidosis, congestive heart failure and poorly controlled diabetes mellitus. One would like to understand better the apparent discrepancy in the record of a patient who was massively edematous on admission but died with progressive dehydration.

My diagnoses are severe hypertension, with congestive heart failure and uremia, and diabetes mellitus, which may well have contributed to the hypertension and renal disease. Hypertensive and diabetic retinopathy were present. The possibility of a pheochromocytoma would have to be considered in light of the history.

DR. DANIEL S. ELLIS: I was convinced that this patient had severe impairment of renal function, but nothing we did seemed to improve this. We wondered whether we were dealing with a chronic pyelonephritis or a chronic glomerulonephritis. Diabetes was present but was well controlled. The hypertension was severe, and she remained in chronic heart failure during most of the hospital stay; it is evident that we were completely unsuccessful in restoring cardiac compensation as we had been in restoring renal compensation. In spite of the long history I favored the diagnosis of Kimmelstiel–Wilson's disease, hypertensive heart disease, with failure, and diabetes mellitus. I did not seriously consider the possibility of a pheochromocytoma.

CLINICAL DIAGNOSES

Kimmelstiel–Wilson's disease.
Hypertensive heart disease, with failure.
Diabetes mellitus.

DR. ALEXANDER LEAF'S DIAGNOSES

Severe hypertension, with congestive heart failure and uremia.
Diabetes mellitus.
?Pheochromocytoma.

ANATOMICAL DIAGNOSES

Pyelonephritis, chronic, severe and acute, with abscess formation.
(Uremia.)
Cardiac hypertrophy, hypertensive type.
Bronchopneumonia.
Hydrothorax, right.
Pericarditis, acute (uremic).
(Diabetes mellitus.)
Parathyroid hyperplasia, secondary.
Splenomegaly.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: At autopsy the lungs weighed 600 gm. and were generally clear except for a few scattered areas of hemorrhage. On microscopical examination such areas showed intra-alveolar hemorrhage and fibrinous exudate, both of which are probably best explained by uremia. There was also an occasional focus of bronchopneumonia. The right pleural cavity contained 700 cc. of clear, serous fluid. The pericardial sac also contained a small amount of fibrinous exudate, which, again, was probably an expression of uremia. The heart was moderately enlarged, weighing 460 gm., the hypertrophy being chiefly of the left ventricle. This weight of the heart fits very well with the 450-gm. average reported by Weiss and Parker* in patients suffering from the type of kidney disease found in this patient, in contrast to 600 gm. for a group with malignant nephrosclerosis. There was moderate coronary-artery sclerosis. The liver was normal on gross and microscopical examination, and no explanation was found for the history of jaundice in the past. Microscopical examination of the pancreas showed slight to moderate hyalinization of many of the islands of Langerhans. The adrenal glands were normal.

The findings of chief interest were in the kidneys, which were small, of about equal size and together weighed 170 gm. They demonstrated grossly and microscopically all the usual features of chronic pyelonephritis — severe interstitial fibrosis, with scattered collections of lymphocytes, atrophy of tubules, dilated tubules containing colloid casts and hyalinized glomeruli. Superimposed on this more chronic process was an acute pyelonephritis, with scattered abscesses. In addition there was severe arteriolar sclerosis, probably secondary to the chronic renal disease. Intercapillary glomerulosclerosis was not observed. The parathyroid glands showed moderate hyperplasia, again reflecting the chronic renal lesion. In accordance with Dr. Tracy B. Mallory's finding, some years ago, that pyelonephritis was a common cause of splenomegaly, the spleen, which clinically was just palpable, weighed 350 gm.

*Weiss, S., and Parker, F., Jr. Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine* **18**:221-315, 1939.

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CAVEAT SOLLICITATOR

THE Committee on Mercantile Affairs of the Great and General Court of Massachusetts has reported a new bill, S745, relative to the solicitation of funds for charitable purposes. The bill is based on the report of a joint special committee established for the "purpose of investigating the fund raising campaigns of certain charitable, educational and historical organizations, excluding all religious institutions, with a view to protecting the public from unscrupulous promoters and to assure adequate protection and encouragement for fund raising campaigns conducted by bona fide organizations."

S745, if accepted, will require the filing with the city clerk or the attorney general, by the persons soliciting funds, of certain information. Included is the identity of the organization for which funds are to be raised, the purpose for which they will be used, the names of persons having custody of the funds and of their distribution, the methods of solicitation, the duration of the drive, the identification of paid promoters, and various other pertinent information.

The bill calls for the keeping of records of solicitors and the amounts collected by each, and, thirty days after the solicitation, the filing of information regarding the amount of funds collected, the amount paid for expenses, including salaries or commissions of solicitors and promoters, and the amount to be given to the charity. The only exclusions from the provisions of the bill are solicitations for or by churches or other religious organizations, those conducted "exclusively among the members of any organization by the members thereof," and those where the gross amount to be raised will not exceed $1000.

This bill, if passed and implemented, will have the effect of eliminating or reducing in Massachusetts unworthy causes as well as those that are strictly fraudulent. It will reveal to the general public, to whom the information will be available, certain pertinent data that will indicate not only the relative success of each campaign, but the efficiency and the economy with which it was conducted.

The public will still have to choose, among the persuasive arguments of the barkers, the side shows in which it wants to spend its surplus charity dollars. For United Community Services, regardless of those who do not wish to enter it, remains the Big Top — the three-ring charity circus where one gets, or gives, the most for his money.

United Community Services, unfortunately, has more competition — some of it almost ruthless — than it can afford to meet. Each year it must compete with some dozen major national appeals as well as a host of minor ones, to say nothing of the local assaults upon the loose-lipped pocketbook, ranging from the postman's invitation to the ball to the church and the community hospital.

Would that the legislature could curb some of these contributory causes also, before the geese that lay the golden tributes are reduced to the state of laying goose eggs in fact!

A SCIENTIFIC PERSPECTIVE

MANY persons recently received a brochure entitled "A Scientific Perspective on the Cigarette Controversy" emanating from the Tobacco Industry Research Committee.[1] The title is pretentious, for the publication seems rather a series of testimonials than a scientific study. Deprecating the general significance of smoking in relation to lung cancer, the 18-page brochure is actually unscientific in that it glosses over rather than meets the important contrary point of view. Furthermore, it is also unscientific in that the authors remain unsigned and unidentified, except as they comprise the "Tobacco Industry Research Committee"; as long as they remain anonymous

their qualifications to sift the evidence and arrive at a scientific perspective are hidden.

A section entitled "Vital Statistics" includes the summary of an article published in the *Journal*[2] that emphasizes the low incidence of cancer of the lung in persons screened primarily for tuberculosis; the section also gives 4 tables from *Vital Statistics of the United States* that have very little bearing on the "cigarette controversy." Absent are easily accessible statistics, graphs and tables.[3-5] Some such data are indispensable to any scientific evaluation of the cigarette controversy and form the basis of the evidence that the association of cigarette smoking and lung cancer is "so strong as to be considered proof within the everyday meaning of the word."[6]

The article in the *Journal* referred to above[2] describes incidental results in the way of cancer detection that accrued from a program primarily devised for tuberculosis screening. To make very much of the fact that only 39 of 500,000 persons studied for tuberculosis were found to have lung cancer is to gloss over limitations inherent in such a survey. The great majority of persons examined for tuberculosis are expectedly under forty-five years of age — the article in question does not specify the age structure of the population studied — whereas the great majority of persons with detectable pulmonary cancer are over forty-five years of age. Moreover, the number of cases of cancer found through any such transitory study is no index of the number of cases of lung cancer that may occur in the lifetimes of those surveyed; the survey does not test the risks of light or heavy smoking, of inhaling or not inhaling and of the accessory influence of dusty or smoky atmospheres or "cocarcinogens."

Some of the brochure is devoted merely to statements of physicians who have kind words to say about cancer and smoking; thus, a chest specialist is quoted from a 1950 newspaper as stating, "I don't believe smoking plays much part at all in lung cancer," and "a surgeon who asked to remain unnamed declared that 'what strikes one forcibly is that smoking is so prevalent that there would be a lot more lung cancer if this were the cause.' "

The validity of the association of smoking with cancer of the lung has been attested by careful statistical studies[3,5] — most recently by Breslow and his coworkers,[7] who have evaluated the problem in relation to job occupations as well as smoking habits and found an accessory influence of dusts (asbestos in steam fitters, for example) and fumes (among arc welders). Not only is the basic relation to the number of cigarettes smoked confirmed but also the lack of this relation to pipe and cigar smoking carries a clear implication that inhaling is an important factor deserving of further study. "Very few smokers of pipes or cigars inhale but many cigarette smokers do."[8]

Evidence points clearly to the need for more impartial, carefully planned clinical, epidemiologic and laboratory investigations of the relation of smoking and smoke to cancer of the upper respiratory tract, especially studies made by university and medical scientists and established agencies of health. No responsible investigator should embellish his interpretation of risks to society any more than the responsible roentgenologist or thoracic surgeon should instill unwarranted fears into his patients. Each kind of specialist has an obligation to present sober facts in the perspective of his experience, with gravity, rigid honesty and temperate objectivity.

If there is no place for the missionary who has prejudged the issue of smoking and found too simply that "smoking causes cancer," so too there is no place in this arena for the glossing over of the suspected hazard — and it is considered real[6] — by the presentation of carefully selected evidence. Science judges only on the basis of all the facts — those unfavorable as well as those favorable to any hypothesis. To treat the "controversy" as though it were a fine point of law or a problem that can be resolved by the special skills of advertising is to throw dust in the eyes of the American public.

Since publication of the brochure a press release of the Tobacco Industry Research Committee announces in part that "the important thing is to recognize the urgent need to explore every scientific avenue which could lead to discovery of the cause of lung cancer." The statement that the Committee "has pledged financial aid and assistance to a research effort into all phases of tobacco use and health" and that it "is now engaged in careful development of a program of research grants to be made to recognized medical and scientific institutions" gives hope of a co-operative venture aiming toward a scientific perspective — in the customary definition. Scientific means "conducted or systematized after the manner of science; applying expert knowledge or technical skill." Perspective is more difficult to define; one meaning is "the interrelation in which parts of an object are mentally viewed."

References

1. *A Scientific Perspective on the Cigarette Controversy.* 18 pp. New York: Tobacco Industry Research Committee, 1954.
2. McNulty, J. M. Clinical follow-up study of 398 patients suspected of having lung cancer discovered in Boston chest x-ray survey. *New Eng. J. Med.* **250**:14-17, 1954.
3. Levin, M. L., Goldstein, H., and Gerhardt, P. R. Cancer and tobacco smoking: preliminary report. *J.A.M.A.* **143**:336-338, 1950.
4. Doll, R., and Hill, A. B. Smoking and carcinoma of lung: preliminary report. *Brit. M. J.* **2**:739-748, 1950.
5. Sadowsky, D. A., Gilliam, A. G., and Cornfield, J. Statistical association between smoking and carcinoma of lung. *J. Nat. Cancer Inst.* **13**:1237-1258, 1953.
6. Cancer of lung. *New Eng. J. Med.* **249**:465, 1953.
7. Breslow, L., Hoaglin, L., Rasmusen, G., and Abrams, H. K. Occupations and cigarette smoking as factors in lung cancer. *Am. J. Pub. Health* **44**:171-181, 1954.
8. Cigarettes and cancer. *Am. J. Pub. Health* **44**:254, 1954.

RELIGION IN MEDICINE

Ambroise Pare, it will be remembered, almost invariably ended his operative notes with the statement, "I dressed him and God healed him." The aphorism may be seen today over the entrance of the

ancient Hôtel Dieu in Paris, founded about the year 660, such an inscription being quite a natural selection since Paré was house surgeon *(compagnon chirurgien)* there for three years.

Christian Science and some of the schools of New Thought seem to place all their faith in the divine healing of wounds and illnesses, usually to the exclusion of modern medical science. On the other hand some physicians may not realize the power of religious faith in helping their patients to get well. Surely, religion and medicine can and should work together. Christian Scientists have not infrequently been discovered in an advanced stage of cancer when they might have been cured by competent surgery early in the disease. Patients have also been known to die when it is probable that more faith in God would have led to recovery. Everyone, therefore, should strive toward a better working together of religion and medicine, physicians in particular endeavoring to restore their patients' faith.

An excellent example has been set by President Eisenhower, whose inaugural prayer has led the nation to renewed religious faith at a time when atomic weapons threaten the entire world. This prayer cannot be repeated too often:

> Almighty God, as we stand here, at this moment, my future associates in the executive branch of the government join me in beseeching that Thou will make full and complete our dedication to the service of the people in this throng and their fellow citizens everywhere.
>
> Give us, we pray, the power to discern clearly right from wrong, and allow all our works and actions to be governed thereby and by the laws of this land.
>
> Especially we pray that our concern shall be for all the people, regardless of station, race, or calling. May co-operation be permitted and be the mutual aim of those who, under the concept of our Constitution, hold to differing political beliefs, so that all may work for the good of our beloved country and for Thy glory. Amen.

President Pusey of Harvard University is also emphasizing religion by his interest in the Divinity School. In 1947 a commission was set up "to make a study of the School's condition with the obligation to report findings and make recommendations."[1] Its opinion was that the School should be reorganized and given new strength. It pointed out that "to seek what is true is to engage in a moral and spiritual as well as an intellectual quest." President Pusey considers it essential that the School be brought up to a standing and position comparable to that held by Harvard's other professional schools. "Though much remains to be done completely to effect this in the years immediately ahead, I am happy to be able to report that this effort stimulated by the Overseers eight years ago is now strongly going ahead." Mr. Pusey is the first president since Eliot to deliver a major address at the Divinity School[2]; in the course of it he criticized the idea that society can be a substitute for God, and that knowledge and good works are enough:

> This faith will no longer do . . . Events of the 20th century have made its easy optimism unpalatable . . . It is leadership in religious knowledge, and even more, in religious experience . . . of which we now have a most gaping need.

The United States is going through a period of unprecedented material prosperity. It is a welcome sign that its leaders recognize the importance of moral and spiritual experience.

The place of religion in medicine is too fundamental to need comment. It is also too important to be passed over lightly. Religion needs medicine, and medicine needs religion.

References

1. *Harvard University. The President's Report, 1952-1953.* 15 pp. Cambridge: Harvard University Press, 1953.
2. Unconquered frontier. *Time* **63** (No. 9, March 1):58-64, 1954.

PASSANO FOUNDATION AWARD

THE Passano Foundation Award for 1954 has been bestowed on Dr. Homer W. Smith, professor of physiology at New York University College of Medicine, for his contribution to knowledge of the physiology of the kidney during the last twenty years. Dr. Smith thus joins the ranks of an impressive number of eminent recipients, including the late Edwin J. Cohn, the first to be honored (1945), and John F. Enders, the most recent (1953) holder of the award.

Dr. Smith's work in renal physiology matches the record of his distinguished predecessors. His pioneer studies formed the basis of the tests of kidney function now used routinely throughout the world and also of the development of surgical technics that have made possible many routine operations on the organ. His book, *The Kidney: Structure and function in health and disease,* is universally recognized as a classic and authoritative work on the subject; a more recent volume, *From Fish to Philosopher,* gives an original and valuable description of evolution in terms of the kidneys.

As in all the years since the Passano Foundation first honored outstanding contributors to clinical science and research, the selection of the recipient this year is a source of general satisfaction. Dr. Smith is congratulated on this recognition of his achievements, and the Foundation is commended for its continued encouragement of advances in medicine and clinical investigation.

Scarcely do we take up a public journal, but we find a record of the injurious effect of the "spirit-rapping, or manifestation," upon some deluded individual. The insane hospitals are becoming tenanted by these individuals, and whole families have been made wretched by this strange infatuation.

Boston M. & S. J., *May 31, 1854*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Gardner	June 1	Carter R. Rowe, M.D.
Haverhill	June 2	William T. Green, M.D.
Greenfield	June 3	Charles L. Sturdevant, M.D.
Salem	June 7	Paul W. Hugenberger, M.D.
Brockton	June 10	George W. Van Gorder, M.D.
Lowell	June 11	Albert H. Brewster, M.D.
Worcester	June 11	John W. O'Meara, M.D.
Lynn*	June 14	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Springfield	June 15	James D. Fisher, M.D.
Pittsfield	June 16	Edward J. Coughlin, Jr., M.D.
Hyannis	June 24	Paul W. Norton, M.D.
Fall River	June 28	David S. Grice, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	June 1, 8, 15, 22, 29
Fitchburg	June 2, 9, 16, 23

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

NOTICES

Dr. Knowles B. Lawrence announces the removal of his office from 1180 Beacon Street to 1683 Beacon Street, Brookline.

FRAMINGHAM GENERAL HOSPITAL LECTURE

Dr. Joseph Doyle, assistant clinical professor of obstetrics, Tufts College Medical School, will deliver a lecture on the subject "A New Physiological Approach to the Problem of Dysmenorrhea" at the Framingham General Hospital, 228 Concord Street, Framingham, on Monday, June 7, at 8:30 p.m.

SOCIETY MEETINGS AND CONFERENCES

May 31–June 3. American Urological Association. Page xvii, issue of July 23.

June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.

June 11–13. American Electroencephalographic Society. Page 748, issue of April 29.

June 15–17. American Society of Medical Technologists. Page 444, issue of March 11.

June 14–16. American Neurological Association. Page 540, issue of March 25.

June 15–18. Medical Library Association. Page 491, issue of March 18.

June 17–19. American Geriatrics Society. Page 266, issue of February 11.

June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.

June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.

June 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.

July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

July 25–29. International Cancer Congress. Page 914, issue of November 26.

July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

August 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

August 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

October 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

December 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JUNE 3

Thursday, June 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
11:00 a.m. Thoracic Conference. The Relationship of Epidermoid Carcinoma in Situ and Its Relation to Carcinoma of the Lung. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
*3:30 p.m. Pathological Conference. Veterans Administration Hospital, Manchester, New Hampshire.

Friday, June 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:00–11:00 a.m. Complications on Surgical Service during May. Dr. W. R. Bosien. Veterans Administration Hospital, Room 132, White River Junction, Vermont.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Medical Conference, Serum Lipoproteins and Atherosclerosis. Dr. A. T. Crocker. Ward C, Veterans Administration Hospital, White River Junction, Vermont.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

Saturday, June 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Stress Reactions following Operations on Bones and Joints. Dr. Philip D. Wilson. Hartford Hospital, Hartford, Connecticut.
*11:00 a.m.–12:00 m. Intermediary Metabolism. Dr. G. H. Stueck. Veterans Administration Hospital, Room 132, White River Junction, Vermont.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek, Pratt Auditorium, New England Center Hospital.

Monday, June 7

Sixty-Seventh Annual Session of the American Orthopaedic Association. Mount Washington Hotel, Bretton Woods, New Hampshire.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinical Pathological Conference. Drs. MacMahon and Baty. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.

Tuesday, June 8

Sixty-Seventh Annual Session of the American Orthopaedic Association. Mount Washington Hotel, Bretton Woods, New Hampshire.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Notices concluded on page xxv)